

	L #	Hits	Search Text
1	L2	74	(bispecific or heteroantibody).clm.
2	L3	4631	macrophage and (tumor or cancer)
3	L4	26	2 and 3
4	L5	71	424/136.1.ccls.
5	L6	20	5 and 2
6	L7	17	5 and 3
7	L8	1305	530/388.7,387.3,388.22,388.8.ccls.
8	L9	219	8 and 3
9	L10	46674	tumor or cancer
10	L11	219	10 and 9
11	L12	119419	bispecific or heteroantibody or hetero\$6
12	L13	146	12 and 11
13	L14	945	cd64 or cd68 or hla-dr or hladr or max1
14	L15	35	14 and 13

=> d his

(FILE 'HOME' ENTERED AT 19:08:01 ON 27 SEP 2000)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 19:08:48 ON 27 SEP 2000

L1 54 S ((CHOKRI M.) OR (CHOKRI M) OR (CHOKRI, MOHAMED) OR (CHOKRI,  
M  
L2 240 S ((BARTHOLEYNS J.) OR (BARTHOLEYNS J) OR (BARTHOLEYNS,  
JACQUES  
L3 3750 S BISPECIFIC  
L4 277320 S MACROPHAGE  
L5 16 S L3 AND L4 AND (L1 OR L2)  
L6 6 DUP REM L5 (10 DUPLICATES REMOVED)  
L7 160 S L3 AND L4  
L8 54551 S CD64 OR CD68 OR MAX1 OR HLADR OR HLA-DR  
L9 29 S L7 AND L8  
L10 17 DUP REM L9 (12 DUPLICATES REMOVED)  
L11 2433580 S CANCER OR TUMOR  
L12 90 S L11 AND L7  
L13 58 DUP REM L12 (32 DUPLICATES REMOVED)  
L14 9 S L8 AND L13  
L15 66 S L13 OR L10  
L16 64 DUP REM L15 (2 DUPLICATES REMOVED)

L16 ANSWER 1 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:368550 CAPLUS

DOCUMENT NUMBER: 133:16331

TITLE: Immune cells having predefined biological  
specificity,

INVENTOR(S): comprising chimeric T cell receptor  
Bolhuis, Reinder L. H.; Eshhar, Zelig; Willemsen,  
Ralph A.

PATENT ASSIGNEE(S): Yeda Research and Development Co. Ltd., Israel

SOURCE: PCT Int. Appl., 51 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000031239	A1	20000602	WO 1999-IL622	19991118
W: AU, CA, CN, IL, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.: IL 1998-127142 19981119

AB Immune cells having predefined specificity are obtained by either  
complexing the cells with an antigen-specific MHC-restricted chimeric T  
cell receptor (TCR) or a fragment thereof, or transfecting said cells  
with

an antigen-specific MHC-restricted chimeric TCR gene. The chimeric TCR  
comprises: (i) a first segment comprising either (a) a single-chain TCR  
(scFv-TCR) made of the variable (V) region and, optionally, of either the  
extracellular const. (C) region of an antigen-specific TCR, or of the  
const. region of the Ig kappa light chain (Ck); or (b) a two-chain TCR  
(tcFv-TCR) made of the extracellular variable (V) and const. (C) regions  
of an antigen-specific TCR; and (ii) a second segment comprising a signal

transducing element of an immune cell. The immune cells can be used for example for the treatment of \*\*\*cancer\*\*\*, infectious diseases, autoimmune diseases or graft rejection.

REFERENCE COUNT: 7

REFERENCE(S):

- (1) Cell Genesys Inc; WO 9429438 A 1994
  - (2) Chung, S; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA 1994, V91(26) CAPLUS
  - (3) Eshhar, Z; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA 1993, V90(2), P720 CAPLUS
  - (4) Harvard College; WO 9618105 A 1996
  - (6) Weijtens, M; GENE THERAPY 1998, V5(9) CAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:227691 CAPLUS

DOCUMENT NUMBER: 132:250020

TITLE: \*\*\*Bispecific\*\*\* and trispecific antibodies which specifically react with inducible surface antigens as operational target structures

INVENTOR(S): Lindhofer, Horst

PATENT ASSIGNEE(S): Germany

SOURCE: PCT Int. Appl., 60 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000018806	A1	20000406	WO 1999-EP7095	19990922
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19859110	A1	20000413	DE 1998-19859110	19981221
PRIORITY APPLN. INFO.:			DE 1998-19844157	19980925
			DE 1998-19859110	19981221

AB According to the invention, an intact \*\*\*bispecific\*\*\* or trispecific antibody is provided which comprises at least the following properties: (a) binding to a T cell; (b) binding to at least one antigen on a target cell; (c) binding by the Fc portion thereof (in \*\*\*bispecific\*\*\* antibodies) or by a third specificity (in trispecific antibodies). The antigen can be induced and is not found on the target cell in a non-induced state (normal state) or it exists in a low no. that is insufficient to destroy the target cell. The use of these antibodies for immunotherapy of tumors and infections is discussed.

REFERENCE COUNT: 9

REFERENCE(S):

- (1) Campbell, F; CANCER 1995, V75(11), P2649 MEDLINE
- (2) Campbell, F; CANCER 1995, V75(11), P2649 MEDLINE
- (3) Gsf Forschungszentrum Umwelt; EP 0826696 A 1998
- (4) Gsf Forschungszentrum Umwelt; DE 19649223 A 1998
- (9) Zeidler, R; JOURNAL OF IMMUNOLOGY 1999, V163(3), P1246 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:53887 CAPLUS

DOCUMENT NUMBER: 132:106967

TITLE: Immunological reagent specifically interacting with the extracellular domain of the human zeta chain

INVENTOR(S): Reiter, Christian  
 PATENT ASSIGNEE(S): Connex G.m.b.H., Germany  
 SOURCE: PCT Int. Appl., 79 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000003016	A1	20000120	WO 1999-EP4838	19990709
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9949091	A1	20000201	AU 1999-49091	19990709
PRIORITY APPLN. INFO.:			EP 1998-112867	19980710
			WO 1999-EP4838	19990709

AB The present invention relates to a nucleic acid mol. comprising a nucleic acid sequence encoding at least one complementary detg. region (CDR) of a variable region of an antibody, said antibody specifically interacting with the extracellular domain of the human zeta-chain, said antibody being obtainable by immunizing a rat with Jurkat cells and subsequently with a conjugate comprising a carrier mol. and a peptide comprising the 11 N-terminal amino acids of the rat zeta-chain. Preferably, the (poly)peptide encoded by the nucleic acid mol. of the invention is a monospecific or \*\*\*bispecific\*\*\* antibody. The invention also relates to pharmaceutical compns. comprising i.a. the nucleic acid mol. or antibody of the invention as well as to kits comprising the aforementioned compds. Finally, the invention relates to a method for the detn. of zeta-chain or eta-chain expression on NK-cells, T-cells or precursors thereof employing the antibody of the invention. The antibodies are useful for treatment and prevention of autoimmune diseases, immune deficiency, T cell malignancies, infectious diseases, and for suppression of immune response to avoid graft rejection after organ transplant.

REFERENCE COUNT: 6  
 REFERENCE(S): (2) Helfrich, W; INTERNATIONAL JOURNAL OF CANCER 1998, V76(2), P232 CAPLUS  
 (3) Mack, M; THE JOURNAL OF IMMUNOLOGY 1997, V158(8), P3965 CAPLUS  
 (4) Renner, C; BLOOD 1996, V88(1), P236 CAPLUS  
 (5) Smith, J; THE JOURNAL OF EXPERIMENTAL MEDICINE 1997, V185(8), P1413 CAPLUS  
 (6) Traunecker, A; THE EMBO JOURNAL 1991, V10(12), P3655 CAPLUS  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 64 CAPLUS COPYRIGHT 2000 ACS  
 ACCESSION NUMBER: 2000:506081 CAPLUS  
 DOCUMENT NUMBER: 133:125277

TITLE: Drug targeting with \*\*\*bispecific\*\*\* antibodies  
for the specific coagulation of \*\*\*tumor\*\*\*  
vasculature

INVENTOR(S): Thorpe, Philip E.; Edgington, Thomas S.

PATENT ASSIGNEE(S): Board of Regents, the University of Texas System,  
USA;

SOURCE: The Scripps Research Institute  
U.S., 83 pp., Cont.-in-part of U. S. Ser. No.  
273,567,

abandoned.  
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6093399	A	20000725	US 1995-482369	19950607
US 5855866	A	19990105	US 1994-205330	19940302
PRIORITY APPLN. INFO.:			US 1992-846349	19920305
			US 1994-205330	19940302
			US 1994-273567	19940711

AB Disclosed are various compns. and methods for use in achieving specific  
blood coagulation. This is exemplified by the specific in vivo  
coagulation of \*\*\*tumor\*\*\* vasculature, causing \*\*\*tumor\*\*\*  
regression, through the site-specific delivery of a coagulant using a  
\*\*\*bispecific\*\*\* antibody.

REFERENCE COUNT: 230

REFERENCE(S): (4) Anon; WO 9003801 1990 CAPLUS  
(5) Anon; WO 9005539 1990 CAPLUS  
(6) Anon; WO 9012585 1990 CAPLUS  
(7) Anon; WO 9013300 1990 CAPLUS  
(8) Anon; WO 9212729 1992 CAPLUS  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 5 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:172832 CAPLUS

DOCUMENT NUMBER: 132:212677

TITLE: Kits and methods for the specific coagulation of  
\*\*\*tumor\*\*\* vasculature

INVENTOR(S): Thorpe, Philip E.; Edgington, Thomas S.

PATENT ASSIGNEE(S): The Scripps Research Institute, USA; Board of  
Regents,

the University of Texas System

SOURCE: U.S., 86 pp., Cont.-in-part of U.S. Ser. No. 273,567,  
abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6036955	A	20000314	US 1995-479727	19950607
US 5855866	A	19990105	US 1994-205330	19940302
PRIORITY APPLN. INFO.:			US 1992-846349	19920305
			US 1994-205330	19940302
			US 1994-273567	19940711

AB Disclosed are various compns. and methods for use in achieving specific blood coagulation. This is exemplified by the specific in vivo coagulation of \*\*\*tumor\*\*\* vasculature, causing \*\*\*tumor\*\*\* regression, through the site-specific delivery of a coagulant using a \*\*\*bispecific\*\*\* antibody.

REFERENCE COUNT: 239

REFERENCE(S): (4) Anon; WO 9003801 1990 CAPLUS  
(5) Anon; WO 9005539 1990 CAPLUS  
(6) Anon; WO 9012585 1990 CAPLUS  
(7) Anon; WO 9013300 1990 CAPLUS  
(8) Anon; WO 9212729 1992 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 6 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000211227 EMBASE

TITLE: Differential effect of cytokine treatment on Fc.alpha. receptor I- and Fc.gamma. receptor I-mediated

\*\*\*tumor\*\*\*

cytotoxicity by monocyte-derived macrophages.

AUTHOR: Keler T.; Wallace P.K.; Vitale L.A.; Russoniello C.; Sundarapandiyan K.; Graziano R.F.; Deo Y.M.

CORPORATE SOURCE: Dr. T. Keler, Medarex, Inc., 1545 Route 22 East, Annadale, NJ 08801, United States. tkeler@injersey.com

SOURCE: Journal of Immunology, (2000) 164/11 (5746-5752).  
Refs: 34

ISSN: 0022-1767 CODEN: JOIMA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer

026 Immunology, Serology and Transplantation

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Macrophages represent an important effector cell for Ab-mediated  
\*\*\*tumor\*\*\* therapy. Previous studies have documented that cytokines  
can

influence Fc receptor (FcR) expression and function. In this study we examined the tumoricidal activities of the type I receptors for IgG (Fc.gamma.RI) and the IgA FcR (Fc.alpha.RI) on monocyte-derived macrophages (MDM) cultured in the presence of IFN-.gamma., M-CSF, or GM-CSF. \*\*\*Bispecific\*\*\* Abs were used to target a Her2/neu breast carcinoma cell line, SKBR-3, to Fc.alpha.RI or Fc.gamma.RI on MDM. Although Fc.alpha.RI and Fc.gamma.RI share a common signaling pathway contingent on association with the .gamma.-chain (FcR.gamma. subunit), a marked difference in their efficiency in mediating tumoricidal functions was seen in response to specific cytokines. M-CSF- and GM-CSF-treated MDM mediated efficient phagocytosis of SKBR-3 cells by Fc.alpha.RI and Fc.gamma.RI; however, IFN-.gamma.-treated MDM phagocytosed \*\*\*tumor\*\*\* cells only with the Fc.gamma.RI-directed \*\*\*bispecific\*\*\* Abs. Similarly, IFN-.gamma.-cultured MDM lysed \*\*\*tumor\*\*\* cells more efficiently via Fc.gamma.RI than by Fc.alpha.RI as measured in Ab-dependent cellular cytotoxicity assays. Conversely, GM-CSF-treated MDM mediated more efficient lysis of \*\*\*tumor\*\*\* cells via Fc.alpha.RI than Fc.gamma.RI, while M- CSF-cultured MDM were relatively less

efficient

in mediating Ab-dependent cellular cytotoxicity through either receptor. With the exception of IFN-.gamma.- mediated enhancement of Fc.gamma.RI expression and Fc.gamma.RI .gamma.-chain complexes, the regulation of Fc.gamma.RI- or Fc.alpha.RI-mediated activity occurred without

significant

change in either receptor expression or total complexes with .gamma.

subunit. These data suggest that the efficiency of Ab-mediated  
\*\*\*tumor\*\*\* therapy, which depends on FcR effector cell functions,  
may be modified by the use of specific cytokines.

L16 ANSWER 7 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000217030 EMBASE

TITLE: Purging of epithelial \*\*\*tumor\*\*\* cells from  
peripheral

blood stem cells by means of the \*\*\*bispecific\*\*\*  
antibody BIS-1.

AUTHOR: Schroder C.P.; Kroesen B.-J.; De Leij L.F.M.H.; De Vries  
E.G.E.

CORPORATE SOURCE: E.G.E. De Vries, Division of Medical Oncology, Department  
of Internal Medicine, University Hospital Groningen, P.O.  
Box 30.001, 9700 RB Groningen, Netherlands.  
e.g.e.de.vries@int.azg.nl

SOURCE: Clinical Cancer Research, (2000) 6/6 (2521-2527).

Refs: 41

ISSN: 1078-0432 CODEN: CCREF4

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Peripheral blood stem cell (PBSC) support in breast \*\*\*cancer\*\*\*  
patients allows high-dose chemotherapy, but \*\*\*tumor\*\*\* cell  
contamination of the PBSCs is a potential source of relapse. Specific  
carcinoma cell killing can be obtained by retargeting activated T cells  
with \*\*\*bispecific\*\*\* antibody BIS-1, directed against epithelial  
glycoprotein-2 and CD3. To purge epithelial \*\*\*tumor\*\*\* cells from  
the

PBSCs of breast \*\*\*cancer\*\*\* patients, activation of T cells in PBSCs  
and T-cell retargeting by BIS-1 was studied. PBSCs, obtained by  
leukapheresis after chemotherapy and recombinant human granulocyte  
colony-stimulating factor, were cultured in the presence of PBS,  
interleukin-2, OKT3, or interleukin-2/OKT3 for induction of T-cell  
activation. Subsequently, lysis of epithelial \*\*\*tumor\*\*\* cell lines  
by activated T cells of PBSCs in the presence or absence of BIS-1 was  
assessed with the 51Cr-release assay or immunocytochemical staining. The  
effect on PBSC hematopoietic colony formation (HCF) was evaluated by the  
granulocyte \*\*\*macrophage\*\*\* colony-stimulating units assay. Prior  
to

activation, PBSCs from breast \*\*\*cancer\*\*\* patients contained higher  
levels of CD8+ T cells than peripheral blood from healthy volunteers ( $P < 0.05$ ). The potential of PBSCs to sustain \*\*\*tumor\*\*\* cell lysis was  
increased after all prior activations and was further enhanced by BIS-1.  
Maximal BIS-1 effect was observed after OKT3 activation of PBSCs for 72 h  
( $P < 0.0005$ ), inducing a  $>3$  log depletion of \*\*\*tumor\*\*\* cells. HCF  
was not affected by prior OKT3 activation and/or BIS-1. In conclusion,  
specific \*\*\*tumor\*\*\* cell lysis by PBSCs can be obtained in vitro by  
OKT3 activation and BIS-1 retargeting of T cells, without affecting HCF.  
At present, studies are evaluating this format for future clinical  
application.

L16 ANSWER 8 OF 64 MEDLINE

ACCESSION NUMBER: 2000126063 MEDLINE

DOCUMENT NUMBER: 20126063

TITLE: Transfer of immune complexes from erythrocyte CR1 to mouse

macrophages.  
 AUTHOR: Reinagel M L; Taylor R P  
 CORPORATE SOURCE: Department of Biochemistry, University of Virginia School of Medicine, Charlottesville, VA 22908, USA.  
 CONTRACT NUMBER: AR43307 (NIAMS)  
 SOURCE: JOURNAL OF IMMUNOLOGY, (2000 Feb 15) 164 (4) 1977-85.  
 Journal code: IFB. ISSN: 0022-1767.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 ENTRY MONTH: 200005  
 ENTRY WEEK: 20000502

AB We are developing a potential therapeutic approach for removing pathogens from the circulation of primates in which the pathogen is bound to the complement receptor (CR1) on E using a \*\*\*bispecific\*\*\* mAb complex,

a heteropolymer (HP). We have used mAb this approach to demonstrate that cleared prototype pathogens are localized to, phagocytosed in, and destroyed in the liver. Extension of this work to a clinical setting will require a detailed understanding of the mechanism by which the E-bound immune complex substrates are transferred to fixed tissue macrophages in the liver, the transfer reaction. Therefore, we examined an in vitro system to study this process using bacteriophage phiX174 as a model pathogen. E containing phiX174 (bound via an anti-CR1/anti-phiX174 HP) were incubated with P388D1 murine macrophages, and the two cell types

were separated by centrifugation through Ficoll. Both E and macrophages were then probed and analyzed by RIA or flow cytometry. The results indicate that all three components of the E-bound IC (phiX174, HP, and CR1) were removed from the E and internalized by the macrophages. We found that transfer requires the Fc portion of IgG, because little transfer of phiX174 occurs when it is bound to E CR1 using a HP containing only Fab fragments. These findings, taken in the context of other studies, suggest a general mechanism for the transfer reaction in which Fc receptors facilitate close juxtaposition of the \*\*\*macrophage\*\*\* to the E-bound IC which then allows a \*\*\*macrophage\*\*\* -associated protease to cleave CR1. The released IC are then internalized and processed by the macrophages.

L16 ANSWER 9 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000276981 EMBASE  
 TITLE: Immunotherapeutic perspective for \*\*\*bispecific\*\*\* antibodies.  
 AUTHOR: van Spriel A.B.; van Ojik H.H.; van de Winkel J.G.J.  
 CORPORATE SOURCE: J.G.J. van de Winkel, Immunotherapy Laboratory, Dept. of Immunology/Medarex Europe, University Medical Center Utrecht, Lundlaan 6, 3584 EA Utrecht, Netherlands.  
 j.vandewinkel@lab.azu.nl  
 SOURCE: Immunology Today, (2000) 21/8 (391-397).  
 Refs: 55  
 ISSN: 0167-5699 CODEN: IMTOD8  
 PUBLISHER IDENT.: S 0167-5699(00)01659-5  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 016 Cancer  
 026 Immunology, Serology and Transplantation  
 030 Pharmacology  
 037 Drug Literature Index



LANGUAGE: English

SUMMARY LANGUAGE: English

AB \*\*\*Bispecific\*\*\* antibodies (BsAb) can, by virtue of combining two binding specificities, improve the selectivity and efficacy of antibody-based treatment of human disease. Recent studies underline the importance of both the 'anti-trigger' and 'anti-target' modalities of

BsAb for therapeutic efficacy. Several BsAb induce effective cytotoxicity as well as 'vaccine effects' in vivo. Here, Annemiek van Spriel and colleagues discuss how these results have catalysed renewed efforts to translate BsAb concepts into effective therapies.

L16 ANSWER 10 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000023854 EMBASE

TITLE: The use of \*\*\*bispecific\*\*\* antibodies in

\*\*\*tumor\*\*\*

cell and \*\*\*tumor\*\*\* vasculature directed immunotherapy.

AUTHOR: Molema G.; Kroesen B.J.; Helfrich W.; Meijer D.K.F.; De Leij L.F.M.

CORPORATE SOURCE: G. Molema, Department of Clinical Immunology, Groningen University, Institute for Drug Exploration, Hanzeplein 1, 9713 GZ Groningen, Netherlands. g.molema@med.rug.nl

SOURCE: Journal of Controlled Release, (2000) 64/1-3 (229-239). Refs: 67

ISSN: 0168-3659 CODEN: JCREEC

PUBLISHER IDENT.: S 0168-3659(99)00137-6

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
027 Biophysics, Bioengineering and Medical Instrumentation  
030 Pharmacology  
037 Drug Literature Index  
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

AB To overcome dose limiting toxicities and to increase efficacy of immunotherapy of \*\*\*cancer\*\*\*, a number of strategies are under development for selectively redirecting effector cells/molecules towards \*\*\*tumor\*\*\* cells. Many of these strategies exploit the specificity

of \*\*\*tumor\*\*\* associated antigen recognition by monoclonal antibodies. Using either hybridoma fusion, chemical derivatization or molecular biology technology, antibodies with dual specificity can be constructed. These so called \*\*\*bispecific\*\*\* antibodies (BsAbs) have been used to redirect the cytolytic activity of a variety of immune effector cells

such as cytotoxic T lymphocytes, natural killer cells, neutrophils and monocytes/macrophages to \*\*\*tumor\*\*\* cells. Local administration of BsAbs, either alone or in combination with autologous effector cells, is highly effective in eradicating \*\*\*tumor\*\*\* cells. In contrast, systemic application of BsAb at present is only suitable for adjuvant treatment of minimal residual disease due to poor \*\*\*tumor\*\*\* cell accessibility. As an alternative, angiogenesis related determinants on \*\*\*tumor\*\*\* blood vessels can be exploited for the selective delivery

of effector cells/molecules apart from being used to inhibit angiogenesis. Important advantages of this strategy is that the endothelial cell

associated target epitope(s) are easy accessible. The dependence of  
\*\*\*\*tumor\*\*\* growth on the \*\*\*\*tumor\*\*\* 's blood supply also renders  
\*\*\*\*tumor\*\*\* endothelial cells an attractive target for therapy.

Although

still in its infancy, attacking the \*\*\*\*tumor\*\*\* 's blood supply for  
example by delivering coagulation factors or toxins, or by BsAb directed  
immunotherapies holds great promise for antineoplastic therapy. Copyright  
(C) 2000 Elsevier Science B.V.

L16 ANSWER 11 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:271389 CAPLUS

DOCUMENT NUMBER: 130:280858

TITLE: \*\*\*\*Bispecific\*\*\* molecules directed to  
\*\*\*\*tumor\*\*\* associated glycoprotein-72 and Fc  
receptor

INVENTOR(S): Deo, Yashwant M.; Keler, Tibor

PATENT ASSIGNEE(S): Medarex, Inc., USA

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9919362	A1	19990422	WO 1997-US18428	19971015
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
AU 9747543	A1	19990503	AU 1997-47543	19971015
PRIORITY APPLN. INFO.:			WO 1997-US18428	19971015
AB	The authors disclose the prepn. and biol. activity of ****bispecific*** antibodies which bind to Fc.gamma.RI receptor and the ****tumor*** assocd. glycoprotein 72 (TAG-72). The antibodies were shown to mediate ADCC against TAG-72-expressing target cells by monocytes and neutrophils. These ****bispecific*** antibodies may prove useful in therapy and diagnosis.			
REFERENCE COUNT:	4			
REFERENCE(S):	(1) Dow Chemical Australia; WO 9312231 A 1993			
	(2) Posey, J; AMERICAN ASSOCIATION FOR CANCER			
RESEARCH	1996, V37			
	(3) Russoniello, C; AMERICAN ASSOCIATION FOR CANCER RESEARCH 1997, V38			
	(4) Slavin-Chiorini, D; CANCER RESEARCH 1995, V55(suppl), P5957			

L16 ANSWER 12 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:690871 CAPLUS

DOCUMENT NUMBER: 131:321540

TITLE: Preparation of single chain, multiple antigen-binding  
antibodies and their application for assays,

diagnosis

and therapy

INVENTOR(S): Kontermann, Roland; Sedlacek, Hans-harald; Muller, Rolf  
 PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland Gm.b.H., Germany  
 SOURCE: Eur. Pat. Appl., 22 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 952218	A2	19991027	EP 1999-106176	19990408
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
DE 19816141	A1	19991014	DE 1998-19816141	19980409
DE 19827239	A1	19991223	DE 1998-19827239	19980618
PRIORITY APPLN. INFO.:			DE 1998-19816141	19980409
			DE 1998-19827239	19980618

AB The invention concerns single chain multispecific binding antibodies contg. light and heavy chain fragments of Igs with different specificities, VH(A), VL(B), VH(B), VL(A); the light and heavy chains are tethered together by a linker peptide, L; the VH-VL constructs are linked by a peptide, P; alternatively the mol. contains and effector component E,

that is linked by a binding fragment B; the mol. can be used for immunoassays, diagnosis and therapy. The single chain diabody mol. has the following scheme: NH<sub>2</sub>-VH(A)-L-VL(B)-P-VH(B)-L-VL(A)-B-E-COOH.

Peptide

L contains 5 amino acids; peptide P contains 14-15 amino acids. Peptide B

is a protease cleavage sequence, e.g. PSA, cathepsin. Typical specificities of A and B are: target cell, cell membrane, lymphocytes, macrophages, endothelial cells, \*\*\*tumor\*\*\* cells, cytokines, blood coagulation factors, peptide hormones, steroid hormones, histamine, serotonin, etc. Specifity B and/or the effector component can be directed

to an enzyme, fluorescent or radioactive label. The invention also concerns nucleotide sequences coding for the single chain, multiple antigen-binding antibodies (sequences not given), and the 5' start codon of the sequences. Thus a \*\*\*bispecific\*\*\* diabody was constructed to carcinoembryonic antigen (CEA) and E.coli .beta.-galactosidase with the a Myc epitope to 9E10 antibody and a polyhis tag; and expressed in E.coli TG1. The purified protein was 60 kD; 2-300 .mu.g/L protein was fermented.

The protein was used to bind to CEA expressing LoVo cells, detection was performed via .beta.-galactosidase reaction with X-Gal substrate; also in an ELISA it reacted with CEA and .beta.-galactosidase.

L16 ANSWER 13 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.  
 ACCESSION NUMBER: 1999193466 EMBASE  
 TITLE: Preclinical studies combining \*\*\*bispecific\*\*\* antibodies with Cytokine-stimulated effector cells for immunotherapy of renal cell carcinoma.  
 AUTHOR: Elsasser D.; Stadick H.; Stark S.; Van de Winkel J.G.J.; Gramatzki M.; Schrott K.M.; Valerius T.; Schafhauser W.  
 CORPORATE SOURCE: D. Elsasser, Department of Urology, University of Erlangen-Nuremberg, Maximiliansplatz 1, D-91054 Erlangen, Germany. david.elsaesser@rzmail.uni-erlangen.de  
 SOURCE: Anticancer Research, (1999) 19/2 C (1525-1528).

Refs: 16  
 ISSN: 0250-7005 CODEN: ANTRD4  
 COUNTRY: Greece  
 DOCUMENT TYPE: Journal; Conference Article  
 FILE SEGMENT: 016 Cancer  
 030 Pharmacology  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 AB Background: \*\*\*Bispecific\*\*\* antibodies - consisting of a  
 F(ab')-fragment derived from a monoclonal antibody against a  
 \*\*\*tumor\*\*\*  
 epitope as well as of another antibody against a cytotoxic trigger  
 molecule on immune effector cells-can improve the effectiveness of  
 antibody-based \*\*\*tumor\*\*\* therapy. Materials and Methods: We used  
 \*\*\*bispecific\*\*\* antibodies with one specificity against the EGF-  
 receptor,  
 which is overexpressed on the majority of renal cell carcinomas, and  
 another specificity against Fc receptors on human leukocytes (Fc.gamma.RI/  
 \*\*\*CD64\*\*\* ; Fc.gamma.RIII/CD16 and Fc.alpha.RI/CD89). As source of  
 effector cells, whole blood from patients treated with G-CSF, GM-CSF or  
 IL2/IFN-.alpha. was used in 51Cr-release assays using various renal  
 \*\*\*cancer\*\*\* cell lines as \*\*\*tumor\*\*\* targets. Further  
 experiments  
 with Percoll-isolated granulocytes or mononuclear cells from the same  
 donors were performed in order to identify the active effector cell  
 populations. Results: Compared with conventional monoclonal EGF-R  
 directed  
 antibodies (murine IgG2a, humanized IgG1), \*\*\*bispecific\*\*\*  
 antibodies  
 induced significantly enhanced cytotoxicity. Highest amounts of tumour cell  
 killing were observed using whole blood from patients treated with G-CSF  
 or GM-CSF in combination with an [Fc.alpha.RI x EGF-R] \*\*\*bispecific\*\*\*  
 antibody. Under these conditions, granulocytes constituted the most  
 active  
 effector cell population. Conclusion: The combination of myeloid growth  
 factors and \*\*\*bispecific\*\*\* antibodies offer a promising new  
 approach  
 for the treatment of advance renal cell carcinoma.

L16 ANSWER 14 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999373476 EMBASE  
 TITLE: Production and characterization of mice transgenic for the  
 A and B isoforms of human Fc.gamma.RIII.  
 AUTHOR: Amoroso A.R.; Alpaugh R.K.; Barth M.W.; McCall A.M.;  
 Weiner  
 L.M.  
 CORPORATE SOURCE: L.M. Weiner, Department of Medical Oncology, Fox Chase  
 Cancer Center, 7701 Burholme Avenue, Philadelphia, PA  
 19111, United States  
 SOURCE: Cancer Immunology Immunotherapy, (1999) 48/8 (443-455).  
 Refs: 69  
 ISSN: 0340-7004 CODEN: CIIMDN  
 COUNTRY: Germany  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 016 Cancer  
 026 Immunology, Serology and Transplantation  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 AB Fc.gamma. receptor (Fc.gamma.R) engagement is pivotal for many effector

functions of macrophages, polymorphonuclear neutrophils (PMN), and natural killer (NK) cells. Mice transgenic for the A and B isoforms of human (h) Fc.gamma.RIII on macrophages, PMN, and NK cells were constructed to permit

the study of mechanisms and potential in vivo strategies to utilize the cytotoxic effector and antigen-presenting functions of cells expressing the hFc.gamma.R. The present report characterizes the phenotypic and functional expression of hFc.gamma.RIII in transgenic mice derived by crossing hFc.gamma.RIIIA and hFc.gamma.RIIIB transgenic mice. Interleukin-2 (IL-2) induces hFc.gamma.RIII expression by myeloid cells and their precursors, and these transgenic receptors promote in vitro cytotoxicity and anti-hFc.gamma.RIII antibody internalization.

#### Splenocytes

from untreated and IL-2-treated hFc.gamma.RIIIA, hFc.gamma.RIIIB, and hFc.gamma.RIIIA/B mice exhibited enhanced in vitro cytotoxicity toward HER-2/neu-overexpressing SK- OV-3 human ovarian carcinoma cells when incubated with the murine \*\*\*bispecific\*\*\* mAb 2B1, which has specificity for HER-2/neu and hFc.gamma.RIII. These results indicate that hFc.gamma.RIII transgenes are expressed on relevant murine cellular subsets, exhibit inducible up-regulation patterns similar to those seen

in

humans, and code for functional proteins. hFc.gamma.RIII transgenic mice exhibiting specific cellular subset expression will permit the

#### examination

of strategies designed to enhance hFc.gamma.RIII-dependent immunological effector functions and will provide a model system in which to evaluate preclinically potential candidate molecules that recognize hFc.gamma.RIII for the immunotherapy of \*\*\*cancer\*\*\* .

L16 ANSWER 15 OF 64 MEDLINE

ACCESSION NUMBER: 1999332518 MEDLINE

DOCUMENT NUMBER: 99332518

TITLE: A pilot trial of GM-CSF and MDX-H210 in patients with erbB-2-positive advanced malignancies.

AUTHOR: Posey J A; Raspet R; Verma U; Deo Y M; Keller T; Marshall J

CORPORATE SOURCE: L; Hodgson J; Mazumder A; Hawkins M J  
Department of Medicine, Lombardi Cancer Center, Georgetown University Medical Center, Washington, D.C., USA.

SOURCE: JOURNAL OF IMMUNOTHERAPY, (1999 Jul) 22 (4) 371-9.  
Journal code: CUQ.

PUB. COUNTRY: United States  
(CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199912

AB MDX-H210 is a chemically, cross-linked, half-humanized \*\*\*bispecific\*\*\* antibody composed of F(ab') fragment from monoclonal antibody (mAb) H22 that binds to the high-affinity receptor Fc gamma RI and F(ab') of mAb 520C9 that recognizes the erbB-2 (HER2/neu) oncoprotein. In a previous trial, the murine \*\*\*bispecific\*\*\* , MDX-210 at a dose of 7 mg/m2, was well tolerated and activated monocytes and macrophages in vivo in doses as

low as 0.35 mg/m2. In our multidose trial, granulocyte- \*\*\*macrophage\*\*\* colony-stimulating factor, which increases and activates potential effector cells, was given on days 1-4 at 250 micrograms/m2 s.c. and MDX-H210 was given on day 4 weekly for 4 consecutive weeks. Thirteen patients were treated at dose levels of 1, 3.5, 7, 10, 15, and 20 mg/m2

without dose-limiting toxicity. Fever, chills, and rigors occurred during and up to 2 h postinfusion and correlated with the time to peak levels of \*\*\*tumor\*\*\* necrosis factor-alpha (median 88.2 pg/ml; range 15.6-887 pg/ml) and interleukin-6 (median 371 pg/ml; range 175-2,149 pg/ml). By the fourth consecutive week of treatment the side effects and cytokine levels decreased significantly. Human antitumor antibody (HABA) levels were increased by 200- to 500-fold above pretreatment levels in 5 of 11 evaluable patients after 3 weeks of treatment. The monocyte and granulocyte population increased on days 4 and 11 (median 44%; range 18-68% and 42%; 19-71%), respectively, for monocytes and (60%; 43-75% and 74%; 54-82%) on days 4 and 11 for granulocytes. There was a significant decrease in the monocyte populations immediately after MDX-H210 administration (median decrease 73%; range 42-94%) and (52%; 12-72%) on days 4 and 11, respectively. Ten patients completed 4 weeks of treatment. One patient had a 48% reduction in index lesions and six patients had stable disease at the time of evaluation. Three patients progressed before the fourth week. The therapy was generally well tolerated with toxicity, primarily, limited to the days of treatment.

L16 ANSWER 16 OF 64 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1999:534217 BIOSIS  
DOCUMENT NUMBER: PREV199900534217  
TITLE: Immunotherapy with the \*\*\*bispecific\*\*\* antibody MDX-H210 (anti-HER2 X anti- \*\*\*CD64\*\*\* ) combined with GM-CSF in HER2 positive hormone resistant prostatic \*\*\*cancer\*\*\*  
AUTHOR(S): James, N. D. (1); Atherton, P. J. (1); Howie, A. J. (1); Tchekmedyian, S.; Curnow, R. T.  
CORPORATE SOURCE: (1) CRC Institute for Cancer Studies, University of Birmingham, Birmingham UK  
SOURCE: European Journal of Cancer, (Sept., 1999) Vol. 35, No. SUPPL. 4, pp. S343-S344.  
Meeting Info.: ECCO 10: The European Cancer Conference Vienna, Austria September 12-16, 1999 Federation of European Cancer Societies  
. ISSN: 0959-8049.  
DOCUMENT TYPE: Conference  
LANGUAGE: English

L16 ANSWER 17 OF 64 MEDLINE

ACCESSION NUMBER: 1999332510 MEDLINE  
DOCUMENT NUMBER: 99332510  
TITLE: Large-scale production of natural cytokines during activation and expansion of human T lymphocytes in hollow fiber bioreactor cultures.  
AUTHOR: Lamers C H; Gratama J W; Luider-Vrieling B; Bolhuis R L; Bast E J  
CORPORATE SOURCE: Department of Clinical and Tumor Immunology, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands.  
SOURCE: JOURNAL OF IMMUNOTHERAPY, (1999 Jul) 22 (4) 299-307.  
Journal code: CUQ.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199912  
ENTRY WEEK: 19991201  
AB We studied the large-scale production of a variety of natural cytokines

during the activation and expansion of human T lymphocytes in a hollow fiber bioreactor culture system. Peripheral blood mononuclear cells (PBMC) were activated using phytohemagglutinin plus recombinant interleukin-2 (IL-2). Phytohemagglutinin was either present in the hollow fiber bioreactor during the entire 15-16-day culture period or only during the 20-h preactivation of the PBMC in culture bags. The expanding T lymphocytes were mainly CD3+, 8+ and exerted maximal natural, activated, \*\*\*bispecific\*\*\* monoclonal antibody-redirceted and lectin-dependent cytolytic activities between days 9 and 13 of culture. IL-1 and IL-4 were only produced in low amounts. IL-8 and lymphotoxin were primarily produced during the first week of culture. Harvest of the hollow fiber bioreactor culture supernatant at the time of peak cytokine concentration would have yielded per 10(8) PBMC input between 3.7 and 4.9 micrograms of IL-8 (at days 2 or 3), and between 0.02 and 0.5 microgram of lymphotoxin (at days 6 or 7). \*\*\*Tumor\*\*\* necrosis factor-alpha and IL-6 were produced during the entire culture period of 15 or 16 days: per 10(8) PBMC input, between 0.1 and 0.4 microgram of \*\*\*tumor\*\*\* necrosis factor-alpha (at days 2 or 3) and between 0.03 and 0.5 microgram of IL-6 (at days 15 or 16). Production of interferon-gamma and granulocyte- \*\*\*macrophage\*\*\* colony-stimulating factor started from initiation of cultures onwards to reach peak levels at the end of the 15- or 16-day culture period, yielding at that time between 2.1 and 17.7 micrograms/ml of interferon-gamma and between 0.4 and 4.2 micrograms of granulocyte- \*\*\*macrophage\*\*\* colony-stimulating factor per 10(8) PBMC input. The production of \*\*\*tumor\*\*\* necrosis factor-alpha, IL-6, interferon-gamma, and granulocyte- \*\*\*macrophage\*\*\* colony-stimulating factor was proportional to the extent of lymphocyte multiplication. These results demonstrate the usefulness of hollow fiber bioreactor cultures to produce natural cytokines during the activation and expansion of predominantly CD3+, 8+ T lymphocytes.

L16 ANSWER 18 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999334939 EMBASE

TITLE: Monoclonal antibodies in \*\*\*cancer\*\*\* treatment: A review of recent progress.

AUTHOR: Alpaugh K.; Von Mehren M.

CORPORATE SOURCE: Dr. K. Alpaugh, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111, United States.  
RK-Alpaugh@fccc.edu

SOURCE: BioDrugs, (1999) 12/3 (209-236).  
Refs: 151

ISSN: 1173-8804 CODEN: BIDRF4

COUNTRY: New Zealand

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer  
023 Nuclear Medicine  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Research advances and promising clinical outcomes with immunotherapeutics has led to a resurgence of incorporating monoclonal antibodies in \*\*\*cancer\*\*\* treatment. Unconjugated, conjugated and multi-target constructs are emerging as a conventional form of therapy along with the

classical trio of surgery, radiation and chemotherapy. The recent major accomplishments in monoclonals include: first, the development of human and chimeric structures negating the induction of humoral responses to murine counterparts which limited use; second, protein engineering has improved the affinity and specificity of the antibody to its target; third, technics have been designed to select monoclonal antibodies imparting a biological consequence (function) following binding; and, lastly, recombinant proteins are being created with multiple epitopic specificities and/or fusion with other biologically active proteins such as toxins and cytokines/growth factors. Clinical efficacy in the treatment

of haematological malignancies has secured a role for monoclonals in routine treatment. Evidence of clinical responses in patients with metastatic solid tumours is leading to the next generation of trials in the adjuvant setting. This paper presents an overview of the clinical experience with monoclonal antibodies in \*\*\*cancer\*\*\* treatment over the past 5 years. Our aim is to highlight the successes and advances, as well as noting limitations of antibody therapeutics. The advances seen support a continued effort to optimise the creation, selection and use of immunotherapeutics in the battle against \*\*\*cancer\*\*\*.

L16 ANSWER 19 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999158916 EMBASE

TITLE: Antibody dependent cellular phagocytosis (ADCP) and antibody dependent cellular cytotoxicity (ADCC) of breast \*\*\*cancer\*\*\* cells mediated by \*\*\*bispecific\*\*\* antibody, MDX-210.

AUTHOR: Watanabe M.; Wallace P.K.; Keler T.; Deo Y.M.; Akewanlop C.; Hayes D.F.

CORPORATE SOURCE: Dr. D.F. Hayes, Lombardi Cancer Center, Georgetown University Medical Center, Research Building E504, 3970 Reservoir Road N.W., Washington, DC 20007, United States. hayesdf@gunet.gerorgetown.edu

SOURCE: Breast Cancer Research and Treatment, (1999) 53/3 (199-207).

Refs: 34

ISSN: 0167-6806 CODEN: BCTRD6

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
016 Cancer  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Background: MDX-210 is a \*\*\*bispecific\*\*\* antibody (BsAb) with specificity for both the proto-oncogene product of HER-2/neu (c-erbB-2) and Fc.gamma.RI ( \*\*\*CD64\*\*\* ). HER-2/neu is overexpressed in malignant tissue of approximately 30% of patients with breast \*\*\*cancer\*\*\*, and Fc.gamma.RI is expressed on human monocytes, macrophages, and IFN-.gamma. activated granulocytes. We investigated phagocytosis and cytolysis of cultured human breast \*\*\*cancer\*\*\* cells by human monocyte-derived macrophages (MDM) mediated by BsAb MDX-210, its partially humanized derivative (MDX-H210), and its parent MoAb 520C9 (anti-HER-2/neu) under various conditions. Materials and Methods: Purified monocytes were cultured with GM-CSF, M-CSF, or no cytokine for five or six days.

Antibody dependent cellular phagocytosis (ADCP) and cytolysis (ADCC) assays were performed with the MDM and HER-2/neu positive target cells (SK-BR-3).

ADCP



was measured by two-color fluorescence flow cytometry using PKH2 (green fluorescent dye) and phycoerythrin-conjugated (red) monoclonal antibodies (MoAb) against human CD14 and CD11b. ADCC was measured with a non-radioactive LDH detection kit. Results: Both BsAb MDX-210 (via Fc.gamma.RI) and MoAb 520C9 (mouse IgG1, via Fc.gamma.RII) mediated similar levels of ADCP and ADCC. ADCP mediated by BsAb MDX-H210 was identical to that mediated by BsAb MDX-210. Confocal microscopy demonstrated that dual-labeled cells represented true phagocytosis. Both ADCP and ADCC were higher when MDM were pre-incubated with GM-CSF than when incubated with M-CSF. Conclusions: BsAb MDX-210 is as active in vitro as the parent MoAb 520C9 in inducing both phagocytosis and cytolysis of MDM. MDX-210 and its partially humanized derivative, MDX-H210, mediated similar levels of ADCP. GM-CSF appears to superior to M-CSF in inducing MDM-mediated ADCC and ADCP. These studies support the ongoing clinical investigations of BsAb MDX-210 and its partially humanized derivative.

L16 ANSWER 20 OF 64 MEDLINE

ACCESSION NUMBER: 1999380234 MEDLINE

DOCUMENT NUMBER: 99380234

TITLE: Gene therapy of B-cell lymphoma with cytokine gene-modified

trioma cells.

AUTHOR: Strehl J; Selmayr M; Kremer J P; Hultner L; Lindhofer H; Mocikat R

CORPORATE SOURCE: GSF-Institut fur Molekulare Immunologie, Munich, Germany.

SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1999 Sep 24) 83 (1) 113-20.

Journal code: GQU. ISSN: 0020-7136.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199911

ENTRY WEEK: 19991104

AB The trioma approach is a new immunotherapeutic strategy for treating B-cell lymphomas. It is based on converting the tumour idiotype to a \*\*\*bispecific\*\*\* immunoglobulin that redirects the idiotype to antigen-presenting cells. We show here that even pre-existing tumours can be eradicated by trioma vaccination, that the trioma approach is superior to vaccination with cytokine gene-modified autologous tumour cells and that there is a synergism between trioma immunisation and GM-CSF gene transfer. Furthermore, we show that the immunising potential of GM-CSF gene-modified autologously lymphoma cells is not as dependent on the cytokine expression level as described for other tumour models, such that even minute expression rates are effective. IL-4 gene transfer in the lymphoma model is considerably less efficient or even ineffective when more sensitive systems are used. Remarkably, trioma-mediated effects are extinguished when IL-4 is expressed by the trioma cell. Copyright 1999 Wiley-Liss, Inc.

L16 ANSWER 21 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999295583 EMBASE

TITLE: GM-CSF as adjuvant for immunotherapy with \*\*\*bispecific\*\*\* antibodies.

AUTHOR: Elsasser D.; Stadick H.; Van de Winkel J.G.J.; Valerius T.

CORPORATE SOURCE: T. Valerius, Division Haematology/Oncology, Department of Medicine III, University Erlangen-Nurnberg, Krankenhausstrasse 12, 91054 Erlangen, Germany. thomas.valerius@med3.med.uni-erlangen.de

SOURCE: European Journal of Cancer, (1999) 35/SUPPL. 3 (25-28).  
 Refs: 17  
 ISSN: 0959-8049 CODEN: EJCAEL  
 PUBLISHER IDENT.: S 0959-8049(99)00086-6  
 COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; Conference Article  
 FILE SEGMENT: 016 Cancer  
 026 Immunology, Serology and Transplantation  
 037 Drug Literature Index  
 005 General Pathology and Pathological Anatomy  
 LANGUAGE: English

L16 ANSWER 22 OF 64 CAPLUS COPYRIGHT 2000 ACS  
 ACCESSION NUMBER: 1998:163620 CAPLUS  
 DOCUMENT NUMBER: 128:229362  
 TITLE: Novel combination preparations and their use in  
 immunodiagnosis and immunotherapy  
 INVENTOR(S): Bohlen, Heribert  
 PATENT ASSIGNEE(S): Viva Diagnostika Diagnostische Produkte G.m.b.H.,  
 Germany; Bohlen, Heribert  
 SOURCE: PCT Int. Appl., 125 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808875	A1	19980305	WO 1997-EP4493	19970818
W: AU, BR, BY, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU, SI, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19634730	A1	19980305	DE 1996-19634730	19960828
DE 19703699	A1	19980806	DE 1997-19703699	19970203
AU 9741193	A1	19980319	AU 1997-41193	19970818
PRIORITY APPLN. INFO.: DE 1996-19634730 19960828				
DE 1997-19703699 19970203				
WO 1997-EP4493 19970818				

AB Combination prepns. comprising 3 components are provided for specific purposes in immunol., diagnosis, and therapy. The combination is based on the universal use of an immunolinker which can link .gtoreq.2 other different components provided with different determinants. The immunolinker may be an inert particle bearing reagents specific for .gtoreq.2 determinants, a \*\*\*bispecific\*\*\* antibody, a protein, etc. One of the other components is a target-specific immunol. reagent bearing an antigenic determinant, e.g. a hapten, epitope, paratope, or idiotope specific for 1 of the linker reagents as well as a target-specific reagent (protein, Ig, antibody, antibody fragment, ligand, lectin, receptor-binding mol., adhesion mol., cytokine, etc.). The 3rd component is a biol. active or detectable substance (enzyme, radiolabel, contrast agent, cytostatic agent, prodrug, adhesion mol., cytokine, ligand, antibody, etc.) bearing a determinant specific for the other reagent on the linker. Thus, mice were immunized with both 2,4-dinitrophenol (DNP) and digoxigenin, and myeloma cells and spleen cells from the immunized mice were fused by the PEG method to provide hybridoma cells which were selected for prodn. of monoclonal antibodies to DNP or digoxigenin.

# Cells

from the 2 hybridoma lines were then fused and selected for prodn. of  
 \*\*\*bispecific\*\*\* antibodies to DNP and digoxigenin. The  
 \*\*\*bispecific\*\*\* antibody was used in combination with a DNP-labeled

## OKT

(anti-CD3) monoclonal antibody and a digoxigenin-labeled anti-CD19  
 monoclonal antibody for incubation with cytotoxic T-cells and Eu-labeled  
 Epstein-Barr virus-immortalized B-cells in a cytotoxic FIA.

L16 ANSWER 23 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:12374 CAPLUS

DOCUMENT NUMBER: 130:51356

TITLE: Method of ex vivo immunizing using heterologous  
 intact

INVENTOR(S): \*\*\*bispecific\*\*\* and/or trispecific antibodies  
 Lindhofer, Horst; Kolb, Hans-Jochem; Zeidler,  
 Reinhard; Bornkamm, Georg

PATENT ASSIGNEE(S): Gsf-Forschungszentrum Fur Umwelt Und Gesundheit,  
 Gmbh,

SOURCE: Germany  
 Eur. Pat. Appl., 19 pp.  
 CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 885614	A2	19981223	EP 1998-110972	19980616
EP 885614	A3	19990113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
DE 19725586	A1	19981224	DE 1997-19725586	19970617
DE 19725586	C2	19990624		
JP 11071288	A2	19990316	JP 1998-170389	19980617
PRIORITY APPLN. INFO.:			DE 1997-19725586	19970617

AB The invention describes a method for ex vivo immunization of human and  
 animal with the following steps: (a) isolation of autologous  
 \*\*\*tumor\*\*\*  
 cells; (b) treatment of \*\*\*tumor\*\*\* cells to prevent their survival  
 after reinfusion; (c) incubation of treated \*\*\*tumor\*\*\* cells with  
 intact heterologous \*\*\*bispecific\*\*\* and or trispecific antibodies.  
 The antibodies have the following properties: binding to T-cells, binding  
 to an antigen from the \*\*\*tumor\*\*\* cells, binding through its Fc  
 fragment (by \*\*\*bispecific\*\*\* antibodies) or through a third  
 specificity (by trispecific antibodies) to Fc-pos. cells.

L16 ANSWER 24 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1998:176147 CAPLUS

DOCUMENT NUMBER: 128:216369

TITLE: Bi- and trispecific antibodies for induction of  
 \*\*\*tumor\*\*\* immunity

INVENTOR(S): Lindhofer, Horst; Kolb, Hans-Jochem; Thierfelder,  
 Stefan

PATENT ASSIGNEE(S): GSF-Forschungszentrum fuer Umwelt und Gesundheit  
 G.m.b.H. Neuherberg, Germany

SOURCE: Ger. Offen., 18 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19710497	A1	19980305	DE 1997-19710497	19970313
DE 19710497	C2	19980709		
DE 19649223	A1	19980305	DE 1996-19649223	19961127
DE 19649223	C2	19980730		
EP 826696	A1	19980304	EP 1997-115190	19970902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 826695	A1	19980304	EP 1997-115188	19970902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 10179151	A2	19980707	JP 1997-238745	19970903
US 5985276	A	19991116	US 1997-922966	19970903
PRIORITY APPLN. INFO.:			DE 1996-19635743	19960903
			DE 1996-19648976	19961126
			DE 1996-19649223	19961127
			DE 1997-19710497	19970313

AB The invention concerns intact \*\*\*bispecific\*\*\* or trispecific antibodies, which can bind simultaneously to the T-cell receptor complex of T-cells, to \*\*\*tumor\*\*\* -assocd. antigens of a \*\*\*tumor\*\*\* cell, and through the Fc fragment of \*\*\*bispecific\*\*\* antibodies to Fc-receptor pos. cells. The use of these antibodies for induction of \*\*\*tumor\*\*\* immunity in humans and animals is discussed.

L16 ANSWER 25 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998075643 EMBASE

TITLE: \*\*\*Bispecific\*\*\* molecules directed to the Fc receptor for IgA (Fc.alpha.RI, CD89) and \*\*\*tumor\*\*\* antigens efficiently promote cell-mediated cytotoxicity of \*\*\*tumor\*\*\* targets in whole blood.

AUTHOR: Deo Y.M.; Sundarapandiyan K.; Keler T.; Wallace P.K.; Graziano R.F.

CORPORATE SOURCE: Dr. Y.M. Deo, Medarex Inc., 1545 Route 22 E, Annandale, NJ 08801, United States. yashdeo@injersey.com

SOURCE: Journal of Immunology, (15 Feb 1998) 160/4 (1677-1686). Refs: 41

ISSN: 0022-1767 CODEN: JOIMA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer

026 Immunology, Serology and Transplantation

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The FcR for IgA (Fc.alpha.RI, CD89) is primarily expressed on cytotoxic immune effector cells. By chemically cross-linking F(ab') fragments of the

FcR for IgA (Fc.alpha.RI)-specific mAb (A77) with \*\*\*tumor\*\*\* Ag-specific mAb (anti-HER2/neu and anti-epidermal growth factor receptor), we have developed \*\*\*bispecific\*\*\* molecules (BSM) that simultaneously bind to respective \*\*\*tumor\*\*\* Ags and Fc.alpha.RI-expressing effector cells in whole blood. These BSM mediated up to 55% of specific lysis of appropriate \*\*\*tumor\*\*\* Ag-expressing target cells (from a variety of tumors) with purified polymorphonuclear leukocytes, monocytes, or whole blood effector cells without

preactivation

with exogenous cytokines. To our knowledge, this is the first demonstration of Ab-dependent cell-mediated cytotoxic activity via Fc.alpha.RI in whole blood. Also, monocyte-derived macrophages mediated phagocytosis of HER2/neu-expressing \*\*\*tumor\*\*\* cells (>95% \*\*\*tumor\*\*\* cell loss). These BSM-mediated cytotoxic activities were completely inhibited by F(ab')<sub>2</sub> of A77, demonstrating the specific role

of

Fc.alpha.RI as a trigger molecule. Furthermore, the binding of these BSM to monocytes or polymorphonuclear leukocytes in whole blood did not induce

modulation of Fc.alpha.RI in the absence of the target Ag. Therefore, immune effector cells may be 'armed' with Fc.alpha.RI-directed BSM in whole blood. These Fc.alpha.RI-directed BSM may offer new treatment options for various malignancies and other disease conditions.

L16 ANSWER 26 OF 64 MEDLINE

ACCESSION NUMBER: 1999066844 MEDLINE

DOCUMENT NUMBER: 99066844

TITLE: \*\*\*Macrophage\*\*\* -targeted killing and vaccines.

AUTHOR: Guyre C A; Fanger M W

CORPORATE SOURCE: Department of Physiology, Dartmouth Medical School, Lebanon, NH 03756, USA.

SOURCE: RESEARCH IN IMMUNOLOGY, (1998 Sep-Oct) 149 (7-8) 655-60. Ref: 17

Journal code: R6E. ISSN: 0923-2494.

PUB. COUNTRY: France

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199905

ENTRY WEEK: 19990503

L16 ANSWER 27 OF 64 MEDLINE

ACCESSION NUMBER: 1998295608 MEDLINE

DOCUMENT NUMBER: 98295608

TITLE: Biological therapy of ovarian \*\*\*cancer\*\*\* : current directions.

AUTHOR: Bookman M A

CORPORATE SOURCE: Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA.

SOURCE: SEMINARS IN ONCOLOGY, (1998 Jun) 25 (3) 381-96. Ref: 155

Journal code: UN5. ISSN: 0093-7754.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, ACADEMIC)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199809

AB Despite recent advances in the chemotherapy of ovarian \*\*\*cancer\*\*\* , the development of alternative therapies that retain activity against drug-resistant tumors remains a high priority. Our knowledge regarding growth factors, cytokines, and the immune response continues to expand, and molecular biology has provided an increased diversity of reagents for clinical evaluation. This review focuses on regulatory targets in ovarian \*\*\*cancer\*\*\* , including Her2/neu (c-erbB2) and other growth factor receptors; interferons, interleukins, and other immunoregulatory

cytokines; cellular adhesion molecules; antigen-specific T lymphocytes and adoptive immunotherapy; choice of monoclonal antibody reagents and advances in antibody engineering, including recombinant single-chain binding sites, chimeric proteins, radioconjugates, cytotoxic drug conjugates, immunotoxins, and \*\*\*bispecific\*\*\* antibodies. Although specific roles for biologic therapy in the management of ovarian \*\*\*cancer\*\*\* have yet to be defined, current priorities for clinical research are reviewed.

L16 ANSWER 28 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998404447 EMBASE

TITLE: Treatment of hepatocellular carcinoma with the cellular \*\*\*tumor\*\*\* vaccines generated by in vitro modification of \*\*\*tumor\*\*\* cells with non gene transfer

approaches.

AUTHOR: Wu S.; Ma J.; Che X.; Liu Y.; Wang H.; Zhao J.; Shen F.; Xie T.; Trojan J.; Wu M.; Guo Y.

CORPORATE SOURCE: Y. Guo, Cancer Immunogene Therapy Program, Sidney Kimmel Cancer Centre, 3099 Science Park Road, San Diego, CA

92121,

SOURCE: United States. yguo@skcc.org  
Advances in Experimental Medicine and Biology, (1998)  
451/-

(283-293).

Refs: 30

ISSN: 0065-2598 CODEN: AEMBAP

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Anti- \*\*\*tumor\*\*\* immune responses are mediated primarily by T cells. Down regulation of major histocompatibility complex (MHC) and the molecules that costimulate the immune responses is associated with defective signaling of \*\*\*tumor\*\*\* cells for T cell activation. In vitro fusion of autologous \*\*\*tumor\*\*\* cells with antigen presenting cells (APCs) or treatment of \*\*\*tumor\*\*\* cells with a combination of cytokines significantly increased the expression of MHC class I and adhesion molecules on \*\*\*tumor\*\*\* cell surfaces that costimulate host immune responses. The hybrid cells generated by fusion of \*\*\*tumor\*\*\* cells with APCs and the \*\*\*tumor\*\*\* cells treated in vitro with a combination of cytokines and pre- incubated with a \*\*\*bispecific\*\*\* monoclonal antibody (bi-Mab) cross-linking antigen on \*\*\*tumor\*\*\* cells to CD28 on T cells, become immunogenic and able to stimulate naive

T

cells with generation of \*\*\*tumor\*\*\* specific cytotoxic T cells both in vitro and in vivo. Immunization with the modified \*\*\*tumor\*\*\* cells

elicits an immune response mediated by both CD4+ and CD8+ T cells. This response protected against a parental \*\*\*tumor\*\*\* cell challenge and cured established tumors. The approach was effective in both low immunogenic and non- immunogenic \*\*\*tumor\*\*\* systems. Modification of \*\*\*tumor\*\*\* cells with \*\*\*tumor\*\*\* :APC fusion or the two-step procedure may provide a strategy for development of \*\*\*tumor\*\*\* vaccines that is effective for \*\*\*cancer\*\*\* immunotherapy.

L16 ANSWER 29 OF 64 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1999:105905 BIOSIS

DOCUMENT NUMBER: PREV199900105905

TITLE: (FcalphaRI X CD20) \*\*\*bispecific\*\*\* antibody in combination with GM-CSF: A novel approach to enhance effector cell recruitment for CD20-directed antibody therapy.

AUTHOR(S): Valerius, T. (1); Stockmeyer, B.; Dechant, M.; Repp, R.; Graziano, R. F.; Kalden, J. R.; Glennie, M.; Van De Winkel,

J. G. J.; Gramatzki, M.

CORPORATE SOURCE: (1) Dep. Med. III, Univ. Erlangen-Nuernberg, Nuernberg Germany

SOURCE: Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 246A.

Meeting Info.: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998 The American Society of Hematology . ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

L16 ANSWER 30 OF 64 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1999:94773 BIOSIS

DOCUMENT NUMBER: PREV199900094773

TITLE: \*\*\*Bispecific\*\*\* antibodies in combination with cytokines for immunotherapy of renal cell \*\*\*cancer\*\*\*

:

AUTHOR(S): In vitro studies comparing promising new approaches. Stadick, H. (1); Valerius, T. (1); Elsaesser, D.; Stark, S.; Glennie, M.; Van De Winkel, J. G. J.; Schafhauser, W.; Gramatzki, M. (1)

CORPORATE SOURCE: (1) Dep. Med. III, Univ. Erlangen-Nuernberg, Erlangen-Nuernberg Germany

SOURCE: Annals of Hematology, (1998) Vol. 77, No. SUPPL. 2, pp. S81.

Meeting Info.: Annual Congress of the German and Austrian Societies of Hematology and Oncology Frankfurt, Germany October 25-28, 1998 Austrian Society of Hematology and Oncology . ISSN: 0939-5555.

DOCUMENT TYPE: Conference

LANGUAGE: English

L16 ANSWER 31 OF 64 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1998:459651 BIOSIS

DOCUMENT NUMBER: PREV199800459651

TITLE: Phase II trial of the \*\*\*bispecific\*\*\* antibody MDX-H210 (anti-Her2/Neu X anti- \*\*\*CD64\*\*\* ) combined with GM-CSF in patients with advanced prostate and renal cell carcinoma that express Her2/neu.

AUTHOR(S): James, N. (1); Atherton, P. (1); Koletsky, A.; Tchekmedyan, N.; Curnow, R.

CORPORATE SOURCE: (1) CRC Inst. Cancer Studies, Birmingham B15 2TH UK

SOURCE: British Journal of Cancer, (1998) Vol. 78, No. SUPPL. 2, pp. 19.

Meeting Info.: Joint Meeting of the British Oncological Association, the Association of Cancer Physicians and the Royal College of Radiologists Nottingham, England, UK July 5-7, 1998 Association of Cancer Physicians

DOCUMENT TYPE: . ISSN: 0007-0920.  
LANGUAGE: Conference  
English

L16 ANSWER 32 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1997:761947 CAPLUS

DOCUMENT NUMBER: 128:33765

TITLE: New antigen presenting cells, a process for preparing the same and their use as cellular vaccines

INVENTOR(S): Chokri, Mohamed; Bartholeyns, Jacques; Romet-Lemonne, Jean Loup

PATENT ASSIGNEE(S): I.D.M. Immuno-Designed Molecules, Fr.

SOURCE: Eur. Pat. Appl., 18 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 808897	A1	19971126	EP 1996-401099	19960521
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CA 2252505	AA	19971127	CA 1997-2252505	19970515
WO 9744441	A1	19971127	WO 1997-EP2703	19970515
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9729615	A1	19971209	AU 1997-29615	19970515
EP 925356	A1	19990630	EP 1997-924012	19970515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000503545	T2	20000328	JP 1997-541583	19970515
PRIORITY APPLN. INFO.: EP 1996-401099 19960521				
WO 1997-EP2703 19970515				

AB The invention relates to macrophages characterized in that they have the following properties: they present on their surface : antigen CD14 with a mean intensity of about 20 to about 200, antigen \*\*\*CD64\*\*\* with a mean intensity of about 20 to about 200. They are substantially devoid

of

the surface antigens CD1a and CD1c. The presence and mean intensities resp. of CD14, \*\*\*CD64\*\*\* and the absence of CD1a and CD1c being for instance detd. by immunofluorescence staining and flow cytometry anal. They present a phagocytosis property such as detd. by the following test: said phagocytosis capacity being evaluated by an uptake of formalin fixed yeast, for example, by culturing macrophages for 2 h, adding yeast in

1/10

macrophages/yeast ratio and incubating at 37.degree.C, 5% CO2 atmosphere for 2-3 h fixing by the May-Grunwald-Giems a (MGG) staining, and the percentage of phagocytic macrophages being quantified for instance by microscopic anal.. They have the property of stimulating the proliferation of allogenic lymphocytes such as detd. by the following

test

: allogenic primary mixed lymphocytes reaction (MLR) was carried out in



96-well microtiter plates by adding different nos. (2x10<sup>3</sup> to 2x10<sup>5</sup> in 100 .mu.l medium/well) of macrophages to 2x10<sup>5</sup> in 100 .mu.l medium/well of allogenic T cells purified from buffy coats and after 5 days incubation at

37.degree.C. Cell proliferation was assessed by a colorimetric method, such as the hydrolysis of tetrazolium salt WST-1 (Boehringer Mannheim, Germany ), (slightly red) to formazan (dark Red).

L16 ANSWER 33 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97284696 EMBASE

DOCUMENT NUMBER: 1997284696

TITLE: \*\*\*Bispecific\*\*\* antibodies for the treatment of tumour

and infectious diseases.

AUTHOR: Drakeman D.L.; Fanger M.W.; Wallace P.K.

CORPORATE SOURCE: D.L. Drakeman, Medarex Inc, 1545 Route 22 East, Annandale, NJ 08801, United States

SOURCE: Expert Opinion on Investigational Drugs, (1997) 6/9 (1169-1178).

Refs: 109

ISSN: 1354-3784 CODEN: EOIDER

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology

016 Cancer

026 Immunology, Serology and Transplantation

030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB \*\*\*Bispecific\*\*\* antibodies are in clinical and preclinical development for the treatment of various cancers and life-threatening infectious diseases. Designed to direct and enhance the body's immune response to specific tumours and pathogens, \*\*\*bispecific\*\*\* antibodies have shown promising results in Phase I and Phase II clinical trials, leading in some cases to complete or partial responses in \*\*\*cancer\*\*\* patients. These \*\*\*bispecific\*\*\* antibodies consist

of

a 'targeting' domain, typically a fragment of a monoclonal antibody that binds to a tumour, linked to a 'triggering' arm that is specific for a molecule capable of mediating a phagocytic or lytic response by macrophages, natural killer cells, T-cells or other effector cells. By mediating an immune assault on tumours or pathogens, \*\*\*bispecific\*\*\* antibodies may also lead to antigen presentation and a vaccine-like response in patients. Over the next few years, we expect several

\*\*\*bispecific\*\*\* antibodies to enter the late stages of clinical trials

and ultimately emerge as new pharmaceutical products.

L16 ANSWER 34 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998005995 EMBASE

TITLE: Immunotherapeutic potential of \*\*\*bispecific\*\*\* antibodies.

AUTHOR: Van de Winkel J.G.J.; Bast B.; De Gast G.C.

CORPORATE SOURCE: J.G.J. Van de Winkel, Dept of Immunology, University Hospital Utrecht, Heidelberglaan 100, 3584 CX Utrecht, Netherlands. J.vandeWinkel@lab.azu.nl

SOURCE: Immunology Today, (1997) 18/12 (562-564).

Refs: 14

ISSN: 0167-5699 CODEN: IMTOD8

PUBLISHER IDENT.: S 0167-5699(97)01167-5  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; (Short Survey)  
FILE SEGMENT: 016 Cancer

026 Immunology, Serology and Transplantation  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB \*\*\*Bispecific\*\*\* antibodies (BsAbs) offer therapeutic potential by targeting tumors or pathogens as well as cytotoxic effector and/or antigen-presenting cells. A recent meeting focused on current issues in the BsAb field.

L16 ANSWER 35 OF 64 MEDLINE

ACCESSION NUMBER: 1998098165 MEDLINE

DOCUMENT NUMBER: 98098165

TITLE: Clinical experience with \*\*\*CD64\*\*\* -directed immunotherapy. An overview.

AUTHOR: Curnow R T

CORPORATE SOURCE: Medarex Inc., Annadale, NJ 08801, USA.

SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1997 Nov-Dec) 45 (3-4) 210-5. Ref: 9

Journal code: CN3. ISSN: 0340-7004.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW LITERATURE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199803

AB The class I IgG receptor (Fc gamma RI or \*\*\*CD64\*\*\* receptor), which is present on key cytotoxic effector cells, has been shown to initiate the destruction of \*\*\*tumor\*\*\* cells in vitro and has been hypothesized to play a role in the destruction of antibody-coated cells such as platelets in idiopathic thrombocytopenia purpura (ITP). This overview summarizes the clinical experience with \*\*\*CD64\*\*\* -directed immunotherapy in \*\*\*cancer\*\*\* patients with the \*\*\*bispecific\*\*\* antibodies MDX-447

[humanized Fab anti- \*\*\*CD64\*\*\* x humanized Fab anti-(epidermal growth factor receptor, EGFR)] and MDX-H210 (humanized Fab anti-DC64 x Fab anti-HER2/neu), and with the anti- \*\*\*CD64\*\*\* monoclonal antibody (mAB)

MDX-33 (H22) in the modulation of monocyte \*\*\*CD64\*\*\* in vivo. In an ongoing phase I/II open-label trial with progressive dose escalation (1-15

mg/m2), patients with treatment refractory EGFR-positive cancers (renal cell carcinoma (RCC), head and neck, bladder, ovarian, prostate

\*\*\*cancer\*\*\* and skin \*\*\*cancer\*\*\* ) are treated weekly with intravenous MDX-447, with and without granulocyte-colony-stimulating factor (G-CSF). MDX-447 has been found to be immunologically active at all

doses, binding to circulating monocytes and neutrophils (when given with G-CSF), causing monocytopenia and stimulating increases in circulating plasma cytokines. MDX-447 is well tolerated, the primary toxicities being fever, chills, blood pressure lability, and pain/ myalgias. Of 36

patients

evaluable for response, 9 have experienced stable disease of 3-6 month's duration. The optimal dose and the maximal tolerated dose (MTD) have yet to be defined; dose escalation continues to define better the dose, toxicity, and the potential therapeutic role of this \*\*\*bispecific\*\*\* antibody. Three MDX-H210 phase II trials are currently in progress, all using the intravenous dose of 15 mg/m<sup>2</sup> given with granulocyte/ \*\*\*macrophage\*\*\* (GM-CSF). These consist of one trial each in the treatment of RCC patients, patients with prostate \*\*\*cancer\*\*\*, and colorectal \*\*\*cancer\*\*\* patients, all of whom have failed standard therapy. At the time of writing, 11 patients have been treated in these phase II trials. Four patients have demonstrated antitumor effects. Patients demonstrating responses include 2 with RCC and 2 with prostate \*\*\*cancer\*\*\*. One RCC patient has had a 54% reduction in size of a hepatic metastatic lesion and the other has had a 49% decrease in the size of a lung metastasis with simultaneous clearing of other non-measurable lung lesions. Regarding the two patients with prostate \*\*\*cancer\*\*\*, one has had a 90% reduction in serum prostate-specific antigen (PSA; 118-11 ng/ml), which has persisted for several months; the other patient with prostate has had a 70% reduction of serum PSA (872 ng/ml to 208 ng/ml) within the first month of treatment. Both patients have also demonstrated symptomatic improvement. In a completed phase I and in ongoing phase I/II clinical trials, patients with treatment-refractory HER2/neu positive cancers (breast, ovarian, colorectal, prostate) have been treated with MDX-H210, which has been given alone and in conjunction with G-CSF, GM-CSF, and interferon gamma (IFN gamma). These trials have been open-label, progressive dose-escalation (0.35-135 mg/m<sup>2</sup>) studies in which single, and more often, multiple weekly doses have been administered. MDX-H210 has been well tolerated, with untoward effects being primarily mild-to-moderate flu-like symptoms. The MTD has not yet been defined. MDX-H210 is immunologically active, binding to circulating monocytes, causing monocytopenia, as well as stimulating increases in plasma cytokine levels. Furthermore, some patients have evidence of active antitumor immunity following treatment with MDX-210. Antitumor effects have been seen in response to MDX-H210 administration; these include 1 partial, 2 minor, and 1 mixed \*\*\*tumor\*\*\* response; 15 protocol-defined stable disease responses have occurred. (ABSTRACT TRUNCATED)

L16 ANSWER 36 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.  
 ACCESSION NUMBER: 97378849 EMBASE  
 DOCUMENT NUMBER: 1997378849  
 TITLE: Lysis of murine B lymphoma cells by transgenic phagocytes via a human Fc.gamma.R1xmurine MHC class II \*\*\*bispecific\*\*\* antibody.  
 AUTHOR: Heijnen I.A.F.M.; Glennie M.J.; Van de Winkel J.G.J.  
 CORPORATE SOURCE: J.G.J. Van de Winkel, Department of Immunology, Heidelberglaan 100, 3584 CX Utrecht, Netherlands  
 SOURCE: Cancer Immunology Immunotherapy, (1997) 45/3-4 (166-170). Refs: 21  
 ISSN: 0340-7004 CODEN: CIIMDN  
 COUNTRY: Germany  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 016 Cancer  
 025 Hematology  
 026 Immunology, Serology and Transplantation  
 037 Drug Literature Index  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

AB The class I IgG receptor (Fc.gamma.RI) on cytotoxic effector cells has been reported to initiate destruction of tumour cells by effector cells in vitro. We are aiming at developing an immunocompetent model to evaluate the cytotoxic capacity of human Fc.gamma.RI for the rejection of tumour cells in vivo. Therefore, we recently generated a transgenic mouse strain expressing human Fc.gamma.RI on monocytes, macrophages, and neutrophils. In these mice, the human receptor is up-regulated by granulocyte-colony-stimulating factor (G-CSF) and is able to trigger cellular responses. Subsequently, in the present study the B cell lymphoma IIA1.6 cell line is selected as a tumour target, and a human Fc.gamma.RI-directed antitumour \*\*\*bispecific\*\*\* antibody (bsAb) is constructed and characterized. Fab' fragments of mAb 22, which bind hFcγRI at an epitope that is distinct from the ligand binding site, were chemically linked to Fab' fragments of rat anti-(mMHC class II antigens) mAb M5/114, yielding bsAb 22xM5/114. This bsAb was able to bind simultaneously to hFc.gamma.RI and mMHC class II antigens in a dose-dependent fashion. Binding of 22xM5/114 to FcγRI was not inhibited in the presence of human IgG. It is important to note that, MHC-class-II-expressing IIA1.6 lymphoma cells were lysed by whole blood from G-CSF-treated transgenic mice in the presence of bsAb 22xM5/114. No lysis by whole blood from non-transgenic mice or from transgenic animals that had not received G-CSF was observed. These results indicate that human Fc.gamma.RI is able to mediate lysis of murine IIA1.6 lymphoma cells by transgenic effector cells via bsAb 22xM5/114. A trial with transgenic mice, evaluating the efficacy of these hFc.gamma.RI-directed bsAb in combination with G-CSF for treatment of IIA1.6 B cell lymphoma, is currently in progress.

L16 ANSWER 37 OF 64 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1997:230398 BIOSIS

DOCUMENT NUMBER: PREV199799529601

TITLE: Fc-alpha-R directed \*\*\*bispecific\*\*\* molecules (BSM) mediate lysis and phagocytosis of \*\*\*tumor\*\*\* cells.

AUTHOR(S): Deo, Y. M.; Sundarpandiyian, K.; Keler, T.; Graziano, R. F.

CORPORATE SOURCE: Medarex Inc., Annandale, NJ 08801 USA

SOURCE: Proceedings of the American Association for Cancer Research

Annual Meeting, (1997) Vol. 38, No. 0, pp. 30.

Meeting Info.: Eighty-eighth Annual Meeting of the

American

Association for Cancer Research San Diego, California, USA April 12-16, 1997

ISSN: 0197-016X.

DOCUMENT TYPE: Conference; Abstract

LANGUAGE: English

L16 ANSWER 38 OF 64 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1997:230396 BIOSIS

DOCUMENT NUMBER: PREV199799529599

TITLE: An intact \*\*\*bispecific\*\*\* antibody induces activation of T-cells and monocytes/macrophages resulting in efficient

killing of \*\*\*tumor\*\*\* cells.

AUTHOR(S): Zeidler, R.; Schmitt, B.; Erndl, S.; Lang, S.; Wollenberg, B.; Lindofer, H.

CORPORATE SOURCE: Dep. Otorhinolayngology, Ludwig-Maximilians-Univ.,  
 Marchioninstr. 15, D-81377 Munich Germany  
 SOURCE: Proceedings of the American Association for Cancer  
 Research  
 Annual Meeting, (1997) Vol. 38, No. 0, pp. 29.  
 Meeting Info.: Eighty-eighth Annual Meeting of the  
 American  
 Association for Cancer Research San Diego, California, USA  
 April 12-16, 1997  
 ISSN: 0197-016X.  
 DOCUMENT TYPE: Conference; Abstract  
 LANGUAGE: English

L16 ANSWER 39 OF 64 CAPLUS COPYRIGHT 2000 ACS  
 ACCESSION NUMBER: 1996:254276 CAPLUS  
 DOCUMENT NUMBER: 124:340904  
 TITLE: Methods and bifunctional ligands for specific  
 \*\*\*tumor\*\*\* inhibition by blood coagulation in  
 \*\*\*tumor\*\*\* vasculature  
 INVENTOR(S): Thorpe, Philip E.; Edgington, Thomas S.  
 PATENT ASSIGNEE(S): Univ. of Texas System, USA; Scripps Res. Inst.  
 SOURCE: PCT Int. Appl., 325 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 9  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9601653	A1	19960125	WO 1995-US7439	19950607
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2194369	AA	19960125	CA 1995-2194369	19950607
AU 9528249	A1	19960209	AU 1995-28249	19950607
AU 702250	B2	19990218		
EP 771216	A1	19970507	EP 1995-923817	19950607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1162267	A	19971015	CN 1995-194801	19950607
BR 9508402	A	19971021	BR 1995-8402	19950607
HU 76970	A2	19980128	HU 1997-84	19950607
JP 10505327	T2	19980526	JP 1995-504299	19950607
PRIORITY APPLN. INFO.:			US 1994-273567	19940711
			WO 1995-US7439	19950607

AB \*\*\*Bispecific\*\*\* binding ligands are provided which bind through a  
 1st  
 binding region to a disease-related target cell, e.g. a \*\*\*tumor\*\*\*  
 cell or \*\*\*tumor\*\*\* vasculature; the 2nd region has  
 coagulation-promoting activity or is a binding region for a coagulation  
 factor. Since \*\*\*tumor\*\*\* vasculature is prothrombotic and is  
 predisposed towards coagulation, these targeted coagulants selectively  
 induce blood coagulation in vessels supplying the \*\*\*tumor\*\*\* and  
 cause death of \*\*\*tumor\*\*\* cells. The \*\*\*bispecific\*\*\* binding  
 ligand may be a \*\*\*bispecific\*\*\* (monoclonal) antibody, or the 2

ligands may be connected by a (selectively cleavable) covalent bond, a chem. linking agent, an avidin-biotin linkage, etc. The target of the 1st binding region may be a cytokine-inducible component, and cytokine may be release in response to a leukocyte-activating antibody; this may be a \*\*\*bispecific\*\*\* antibody which crosslinks activated leukocytes with \*\*\*tumor\*\*\* cells. Alternatively, the target of the 1st binding region may be a component (e.g. E- or P-selectin) which is inducible by thrombin, where thrombin prodn. is induced by administration of a \*\*\*bispecific\*\*\* antibody which binds to a \*\*\*tumor\*\*\* cell and to tissue factor, prothrombin, factor VII/VIIa, factor IX/IXa, etc. Thus, a coaguligand ( \*\*\*bispecific\*\*\* antibody capable of targeting a coagulant to a \*\*\*tumor\*\*\* site) was prepd. by chem. coupling an Fab' fragment from monoclonal antibody B21-2 (which reacts with I-Ad antigen expressed on A20 B-cell lymphoma cells and on the vasculature of C1300 transfectant mouse tumors) with an Fab' fragment from monoclonal antibody 10H10 (which reacts with human tissue factor). Incubation of A20 cells with this \*\*\*bispecific\*\*\* antibody and recombinant human truncated tissue factor resulted in tethering of tissue factor to the cells; plasma added to the A20 cell-tissue factor complex coagulated rapidly. Kits comprising the bifunctional ligand, a 2nd ligand, and optionally a drug for conjunctive therapy are described.

L16. ANSWER 40 OF 64 MEDLINE

ACCESSION NUMBER: 96199419 MEDLINE

DOCUMENT NUMBER: 96199419

TITLE: \*\*\*Bispecific\*\*\* -armed, interferon gamma-primed  
\*\*\*macrophage\*\*\* -mediated phagocytosis of malignant  
non-Hodgkin's lymphoma.

AUTHOR: Ely P; Wallace P K; Givan A L; Graziano R F; Guyre P M;  
Fanger M W

CORPORATE SOURCE: Department of Medicine, Dartmouth Medical School, Lebanon,  
NH 03756, USA.

CONTRACT NUMBER: AI-19053 (NIAID)  
CA-09658 (NCI)  
CA-23108 (NCI)

SOURCE: BLOOD, (1996 May 1) 87 (9) 3813-21.  
Journal code: A8G. ISSN: 0006-4971.

PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer  
Journals

ENTRY MONTH: 199608

AB To show that macrophages can be effectively targeted against malignant B cells, \*\*\*bispecific\*\*\* antibodies (BsAb) were constructed from two antibodies having specificity for the high-affinity Fc receptor for IgG (Fc gamma RI/ \*\*\*CD64\*\*\* ) and the B-cell differentiation antigens CD19 and CD37. Using a flow cytometry-based assay and confocal imaging, we show

that these constructs mediated significant phagocytosis of B lymphocytes by macrophages that could be enhanced with interferon gamma (IFN gamma) and IFN gamma in combination with \*\*\*macrophage\*\*\* colony-stimulating factor. BsAb-dependent phagocytosis was triggered through Fc gamma RI and

could be blocked only by using F(ab')<sub>2</sub> fragments from the parent molecule or by cross-linking Fc gamma RI. BsAb-dependent phagocytosis was not blocked by antibodies to the other Fc receptors, Fc gamma RII and Fc gamma

RIII. Because these antibody constructs bind to an epitope outside the Fc gamma RI ligand binding site, we show that autologous serum, polyclonal IgG, and monomeric IgG1 did not block BsAb-dependent phagocytosis, whereas

autologous serum and the IgG fractions blocked parent molecule monoclonal antibody-dependent phagocytosis due to the avid binding of monomeric IgG to Fc gamma RI. Finally, BsAb-mediated phagocytosis was effective against the malignant B cells of patients with mantle cell lymphoma, prolymphocytic leukemia, and chronic lymphocytic leukemia. Based on these studies, we propose that BsAbs may provide an effective means of immunomodulation for patients with B-cell malignancies.

L16 ANSWER 41 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96134425 EMBASE

DOCUMENT NUMBER: 1996134425

TITLE: FcR .gamma.-chain is essential for both surface expression and function of human Fc.gamma.RI ( \*\*\*CD64\*\*\* ) in

vivo.

AUTHOR: Van Vugt M.J.; Heijnen I.A.F.M.; Capel P.J.A.; Park S.Y.; Ra C.; Saito T.; Verbeek J.S.; Van de Winkel J.G.J.

CORPORATE SOURCE: Department of Immunology, University Hospital Utrecht, Heidelberglaan 100, 3584 CX Utrecht, Netherlands

SOURCE: Blood, (1996) 87/9 (3593-3599).

ISSN: 0006-4971 CODEN: BLOOAW

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 026 Immunology, Serology and Transplantation

029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Most Ig receptors exist as hetero-oligomeric complexes with separate ligand binding (.alpha.) and signal transducing (.beta., .gamma., or .zeta.) subunits. For Fc.gamma.RIIa and Fc.epsilon.RI, association with the FcR .gamma.-chain is essential for surface expression. However, the human high affinity IgG receptor, hFc.gamma.RI, was found to be surface-expressed by itself in transient transfection models. We have now analyzed the integrity of hFc.gamma.RI expression in more detail in

stable transfectants. In vitro we noted that, in the absence of FcR .gamma.-chain, surface expression of hFc.gamma.RI rapidly declined to background levels, in both IIA1.6 B cells and NIH3T3 fibroblasts. The effect of FcR .gamma.-chain on hFc.gamma.RI surface expression in vivo was evaluated by using two newly generated transgenic mouse lines, selectively expressing hFc.gamma.RI on myeloid cells. These transgenic mice were crossed with

FcR

.gamma.-chain-deficient mice. Analysis of blood monocytes and peritoneal macrophages showed that surface expression of hFc.gamma.RI was reduced by .apprx.80%. The remaining .apprx.20% of receptors were still capable of binding IgG-opsonized RBC, suggesting FcR .gamma.-chain not to be

critical

for hFc.gamma.RI ligand-binding capacity. Importantly, however, hFc.gamma.RI signaling capacity was lost in FcR .gamma.-chain-deficient cells. No phagocytosis could be observed using either ligand sensitized (EA-IgG2a) or \*\*\*CD64\*\*\* -targeted erythrocytes (using a

\*\*\*bispecific\*\*\* antibody) in both hFc.gamma.RI transgenic lines.

This

documents the FcR .gamma.-chain to be indispensable for both surface membrane expression and function of human Fc.gamma.RI in vivo.

L16 ANSWER 42 OF 64 MEDLINE

ACCESSION NUMBER: 96427373 MEDLINE

DOCUMENT NUMBER: 96427373

TITLE: Development of a \*\*\*bispecific\*\*\* F(ab')<sub>2</sub> conjugate against the complement receptor CR3 of macrophages and a variant CD44 antigen of rat pancreatic adenocarcinoma for redirecting \*\*\*macrophage\*\*\* -mediated \*\*\*tumor\*\*\* cytotoxicity.

AUTHOR: Somasundaram C; Arch R; Matzku S; Zoller M

CORPORATE SOURCE: Department of Tumor Progression and Immune Defense, German Cancer Research Center, Heidelberg, Germany.

SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1996 Jul) 42 (6) 343-50.

Journal code: CN3. ISSN: 0340-7004.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199701

ENTRY WEEK: 19970104

AB A \*\*\*bispecific\*\*\* F(ab')<sub>2</sub> antibody conjugate (BAC) was constructed against the complement receptor CR3 of macrophages and variant CD44 (CD44v6) antigen of rat pancreatic adenocarcinoma cells to redirect \*\*\*macrophage\*\*\* -mediated \*\*\*tumor\*\*\* cytotoxicity. The Fab' fragments of monoclonal antibodies (mAb) 1.1ASML and OX42, recognizing

the

CD44v6 and the CR3 antigens respectively, were chemically coupled at the hinge region using 5,5'-dithiobis(2-nitrobenzoate). The BAC was characterized in vitro for its specific, dual binding capacity to CD44v6 and CR3 antigens. Although the monovalence of the BAC resulted in lower avidities to both the antigens as expected, it was still able to form stable cross-linkages between \*\*\*tumor\*\*\* cells and macrophages in culture leading to the formation of "clump-like" cell aggregates. The in vitro and in vivo \*\*\*tumor\*\*\* -targeting capacity of the BAC was compared with that of the parental antitumor mAb 1.1ASML, which mediates \*\*\*tumor\*\*\* killing by antibody-dependent cell cytotoxicity. These results showed that, even though the bivalent mAb 1.1ASML did not mediate stable cross-linking of target and effector cells, its Fc-receptor-mediated killing of \*\*\*tumor\*\*\* cells was more effective when compared to the BAC. Thus, this study strongly supports the hypothesis that firm persistent binding between effector and target cells per se is not as important as the choice of trigger molecule used for \*\*\*macrophage\*\*\* activation to redirect their \*\*\*tumor\*\*\*

cytotoxic

potential effectively.

L16 ANSWER 43 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96037950 EMBASE

DOCUMENT NUMBER: 1996037950

TITLE: Antigen targeting to myeloid-specific human Fc.gamma.RI/ \*\*\*CD64\*\*\* triggers enhanced antibody responses in transgenic mice.

AUTHOR: Heijnen I.A.F.M.; Van Vugt M.J.; Fanger N.A.; Graziano R.F.; De Wit T.P.M.; Hofhuis F.M.A.; Guyre P.M.; Capel P.J.A.; Verbeek J.S.; Van de Winkel J.G.J.

CORPORATE SOURCE: Department of Immunology, University Hospital Utrecht, Heidelberglaan 100, 3584 CX Utrecht, Netherlands



SOURCE: Journal of Clinical Investigation, (1996) 97/2 (331-338).  
ISSN: 0021-9738 CODEN: JCINAO  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB Besides their phagocytic effector functions, myeloid cells have an essential role as accessory cells in the induction of optimal humoral immune responses by presenting captured antigens and activating lymphocytes. Antigen presentation by human monocytes was recently found to

be enhanced in vitro through the high-affinity Fc receptor for IgG (Fc.gamma.RI; \*\*\*CD64\*\*\*), which is exclusively present on myeloid cells. To evaluate a comparable role of Fc.gamma.RI in antigen presentation in vivo, we generated human Fc.gamma.RI transgenic mice. Under control of its endogenous promoter, human Fc.gamma.RI was selectively expressed on murine myeloid cells at physiological expression levels. As in humans, expression was properly regulated by the cytokines IFN-.gamma., G-CSF, IL-4, and IL-10, and was up-regulated during inflammation. The human receptor expressed by murine macrophages bound monomeric human IgG and mediated particle phagocytosis and IgG complex internalization. To evaluate whether specific targeting of antigens to Fc.gamma.RI can induce enhanced antibody responses, mice were immunized with an antihuman Fc.gamma.RI antibody containing antigenic determinants. Transgenic mice produced antigen-specific antibody responses with high IgG1 titers and substantial IgG2a and IgG2b responses. These data demonstrate that human Fc.gamma.RI on myeloid cells is highly active in mediating enhanced antigen presentation in vivo, and show that anti-Fc.gamma.RI mAbs are promising vaccine adjuvants.

L16 ANSWER 44 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96030172 EMBASE  
DOCUMENT NUMBER: 1996030172  
TITLE: [ \*\*\*Bispecific\*\*\* antibody H-447 in \*\*\*cancer\*\*\* diseases].  
BISPEZIFISCHER ANTIKORPER H-447 BEI KREBSERKRANKUNGEN.  
SOURCE: Deutsche Apotheker Zeitung, (1996) 136/2 (32-33).  
ISSN: 0011-9857 CODEN: DAZE2  
COUNTRY: Germany  
DOCUMENT TYPE: Journal; (Short Survey)  
FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: German  
SUMMARY LANGUAGE: German

L16 ANSWER 45 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95313186 EMBASE  
DOCUMENT NUMBER: 1995313186  
TITLE: Phase I trial of 2B1, a \*\*\*bispecific\*\*\* monoclonal antibody targeting c-erbB-2 and Fc.gamma.RIII.  
AUTHOR: Weiner L.M.; Clark J.I.; Davey M.; Li W.S.; De Palazzo I.G.; Ring D.B.; Alpaugh R.K.  
CORPORATE SOURCE: Department of Medical Oncology, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111, United States  
SOURCE: Cancer Research, (1995) 55/20 (4586-4593).  
ISSN: 0008-5472 CODEN: CNREA8

COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index  
038 Adverse Reactions Titles

LANGUAGE: English  
SUMMARY LANGUAGE: English

AB 2B1 is a \*\*\*bispecific\*\*\* murine monoclonal antibody (BsMab) with specificity for the c-erbB-2 and Fc.gamma.RIII extracellular domains.

This

BsMab promotes the targeted lysis of malignant cells overexpressing the c-erbB-2 gene product of the HER2/neu proto-oncogene by human natural killer cells and mononuclear phagocytes expressing the Fc.gamma.RIII A isoform. In a Phase I clinical trial of 2B1, 15 patients with c-erbB-2-overexpressing tumors were treated with 1 h i.v. infusions of

2B1

on days 1, 4, 5, 6, 7, and 8 of a single course of treatment. Three patients were treated with daily doses of 1.0 mg/m<sup>2</sup>, while six patients each were treated with 2.5 mg/m<sup>2</sup> and 5.0 mg/m<sup>2</sup>, respectively. The principal non-dose-limiting transient toxicities were fevers, rigors, nausea, vomiting, and leukopenia. Thrombocytopenia was dose limiting at the 5.0 mg/m<sup>2</sup> dose level in two patients who had received extensive prior myelosuppressive chemotherapy. Murine antibody was detectable in serum following 2B1 administration, and its \*\*\*bispecific\*\*\* binding properties were retained. The pharmacokinetics of this murine antibody were variable and best described by nonlinear kinetics with an average t(1/2) of 20 h. Murine antibody bound extensively to all neutrophils and to a proportion of monocytes and lymphocytes. The initial 2B1 treatment induced more than 100-fold increases in circulating levels of

\*\*\*tumor\*\*\* necrosis factor-.alpha., interleukin 6, and interleukin 8 and lesser rises in granulocyte-monocyte colony-stimulating factor and IFN-.gamma.. Brisk human anti-mouse antibody responses were induced in 14 of 15 patients. Several minor clinical responses were observed, with reductions in the thickness of chest wall disease in one patient with disseminated breast \*\*\*cancer\*\*\*. Resolution of pleural effusions and ascites, respectively, were noted in two patients with metastatic colon \*\*\*cancer\*\*\*, and one of two liver metastases resolved in a patient

with

metastatic colon \*\*\*cancer\*\*\*. Treatment with 2B1 BsMab has potent immunological consequences. The maximum tolerated dose and Phase II daily dose for patients with extensive prior myelosuppressive chemotherapy was 2.5 mg/m<sup>2</sup>. Continued dose escalation is required to identify the

maximally

tolerated dose for patients who have been less heavily pretreated.

L16 ANSWER 46 OF 64 MEDLINE

DUPLICATE 1

ACCESSION NUMBER: 95395483 MEDLINE

DOCUMENT NUMBER: 95395483

TITLE: Phase Ia/Ib trial of \*\*\*bispecific\*\*\* antibody MDX-210 in patients with advanced breast or ovarian \*\*\*cancer\*\*\* that overexpresses the proto-oncogene HER-2/neu.

AUTHOR: Valone F H; Kaufman P A; Guyre P M; Lewis L D; Memoli V; Deo Y; Graziano R; Fisher J L; Meyer L; Mrozek-Orlowski M; et al

CORPORATE SOURCE: Department of Medicine, Dartmouth-Hitchcock Medical Center,

Lebanon, NH, USA.

CONTRACT NUMBER: CA23108-15 (NCI)

AI19053 (NIAID)

SOURCE: JOURNAL OF CLINICAL ONCOLOGY, (1995 Sep) 13 (9) 2281-92.  
Journal code: JCO. ISSN: 0732-183X.

PUB. COUNTRY: United States  
(CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE I)  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199512

AB PURPOSE: MDX-210 is a \*\*\*bispecific\*\*\* antibody that binds simultaneously to type I Fc receptors for immunoglobulin G (IgG) (Fc gamma RI) and to the HER-2/neu oncogene protein product. MDX-210 effectively directs Fc gamma RI-positive effector cells such as monocytes and macrophages to phagocytose or kill \*\*\*tumor\*\*\* cells that overexpress HER-2/neu. The goals of this phase Ia/Ib trial were to determine the maximum-tolerated dose (MTD) and/or the optimal biologic dose (OBD) of MDX-210. PATIENTS AND METHODS: Patients with advanced breast or ovarian \*\*\*cancer\*\*\* that overexpressed HER-2/neu were eligible for treatment.

Cohorts of three patients received a single intravenous (IV) infusion of MDX-210 at increasing dose levels from 0.35 to 10.0 mg/m2. RESULTS: Treatment was well tolerated, with most patients experiencing transient grade 1 to 2 fevers, malaise, and hypotension only. Two patients experienced transient grade 3 hypotension at 10.0 mg/m2. Transient monocytopenia and lymphopenia developed at 1 to 2 hours, but no other hematologic changes were observed. Doses of MDX-210 > or = 3.5 mg/m2 saturated > or = 80% of monocyte Fc gamma RI and produced peak plasma concentrations > or = 1 microgram/mL, which is greater than the concentration for optimal monocyte/ \*\*\*macrophage\*\*\* activation in vitro. Elevated plasma levels of the monocyte products \*\*\*tumor\*\*\* necrosis factor alpha (TNF alpha), interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF), and neopterin were observed with maximal levels at doses > or = 7.0 mg/m2. Localization of MDX-210 in \*\*\*tumor\*\*\* tissue was demonstrated in two patients. One partial and one mixed \*\*\*tumor\*\*\* response were observed among 10 assessable patients.

CONCLUSION: MDX-210 is immunologically active at well-tolerated doses. The MTD and OBD is 7 to 10 mg/m2.

L16 ANSWER 47 OF 64 MEDLINE

ACCESSION NUMBER: 1999034945 MEDLINE

DOCUMENT NUMBER: 99034945

TITLE: Monocyte-mediated lysis of acute myeloid leukemia cells in the presence of the \*\*\*bispecific\*\*\* antibody 251 x 22 (anti-CD33 x anti- \*\*\*CD64\*\*\* ).

AUTHOR: Chen J; Zhou J H; Ball E D

CORPORATE SOURCE: Division of Hematology/Bone Marrow Transplantation, University of Pittsburgh Medical Center and Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania 15213, USA.

CONTRACT NUMBER: CA31888 (NCI)

SOURCE: CLINICAL CANCER RESEARCH, (1995 Nov) 1 (11) 1319-25.  
Journal code: C2H. ISSN: 1078-0432.

PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199904

ENTRY WEEK: 19990402

AB Immunotherapy using \*\*\*bispecific\*\*\* antibodies (BsAb) to direct immune effector cells toward target \*\*\*tumor\*\*\* cells has been shown to be effective in a number of studies. Several immune trigger molecules have been characterized. Among them, FcgammaRI appears to play an important role in antibody-dependent cellular cytotoxicity. It is expressed mainly on monocytes, macrophages, and neutrophils under certain clinical situations. The expression of FcgammaRI can be regulated by a variety of cytokines, primarily by IFN-gamma. Recent studies have shown that granulocyte-colony-stimulating factor (G-CSF) and granulocyte-\*\*\*macrophage\*\*\*-colony stimulating factor (GM-CSF) can increase the number of the FcgammaRI-positive monocytes, increase the expression of FcgammaRI on circulating neutrophils after in vivo infusion, and greatly enhance the cytotoxic activity of circulating neutrophils. CD33 is a glycoprotein expressed on the cell surface of mature monocytes, myeloid progenitor cells, and myeloid leukemic blasts, but not on the earliest hematopoietic progenitor cells and other normal tissues. Herein, we

report

the construction of a BsAb, 251 x 22, by conjugating an anti-CD33 mAb (mAb

251) to an anti-FcgammaRI mAb (mAb 22). The BsAb 251 x 22 is capable of enhancing the cytotoxicity of several leukemia cell lines by cytokine-activated monocytes. Our data also show that G-CSF- and GM-CSF-stimulated monocytes can mediate cytotoxicity of target leukemia cells comparable to that of IFN-gamma-stimulated monocytes. The

expression

of FcgammaRI on monocytes after 24-h in vitro incubation with G-CSF and GM-CSF was increased, although not significantly. Prolonged incubation of monocytes with G-CSF for 48 h significantly increased the FcgammaRI expression. Because humanized anti-CD33 and anti-FcgammaRI mAb are available, and because GM-CSF and G-CSF have been used widely for

patients

after chemotherapy to stimulate the recovery of myeloid hematopoiesis, additional clinical development of this project is feasible. A BsAb comprised of humanized anti-CD33 and anti-FcgammaRI could have clinical application in the treatment of myeloid leukemia, especially in the management of minimal residual disease.

L16 ANSWER 48 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96018795 EMBASE

DOCUMENT NUMBER: 1996018795

TITLE: Functional consequences of \*\*\*macrophage\*\*\* infection by human immunodeficiency virus: \*\*\*Bispecific\*\*\* antibody targeting of HIV-1-infected cells to FC.gamma.RI expressing effector cells.

AUTHOR: Mabondzo A.; Le Naour R.; Le Grand R.; Vaslin B.; Benveniste O.; Cheret A.; Raoul H.; Romet-Lemonne J.L.; Dormont D.

CORPORATE SOURCE: Service de Neurovirologie, CEA/DSV/DRM/IPSC B.P.6, 60/68 Avenue de la Division Leclerc, 92265 Fontenay-aux-Roses Cedex, France

SOURCE: Journal of Hematotherapy, (1995) 4/6 (579-585).  
ISSN: 1061-6128 CODEN: JOEMEL

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 004 Microbiology

026 Immunology, Serology and Transplantation

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Human monocytes/macrophages play a major role in pathogenesis of human

immunodeficiency virus (HIV) infection. These cells have been suspected of

acting as a reservoir for the virus and are important in viral dissemination and persistence in infected individuals. Furthermore, several biologic and clinical features indicate that monocytes/macrophages

from HIV-1-seropositive patients have characteristics of an activation status, including the ability to secrete high levels of cytokines. Dysregulation of the cytokine network may influence the level and the consequences of viral replication in infected monocytes/macrophages. Therefore, the development of virus-specific agents that may interfere with viral replication could help to slow down the fatal course of HIV infection. In this article, we try to further quantify the early and late kinetic patterns of the cytokine network during HIV-1 \*\*\*macrophage\*\*\* infection and report the biologic effects of virus-specific \*\*\*bispecific\*\*\* antibody (MDX-240) in HIV-1 \*\*\*macrophage\*\*\* infection.

L16 ANSWER 49 OF 64 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1996:49712 BIOSIS

DOCUMENT NUMBER: PREV199698621847

TITLE: Phase I trial of MDX210 ( \*\*\*bispecific\*\*\* antibody Fc-gamma-RI x HER-2/neu) in combination with G-CSF in patients with breast \*\*\*cancer\*\*\* .

AUTHOR(S): Repp, R. (1); Valerius, T.; Wieland, G.; Oetzel, C.; Deo, Y.; Van De Winkel, J. G.; Kalden, J. R.; Lang, N.; Gramatzki, M.

CORPORATE SOURCE: (1) Dep. Med. III, Univ. Erlangen-Nuernberg, Erlangen Germany

SOURCE: Blood, (1995) Vol. 86, No. 10 SUPPL. 1, pp. 507A.  
Meeting Info.: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995  
ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

L16 ANSWER 50 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95336566 EMBASE

DOCUMENT NUMBER: 1995336566

TITLE: A human Fc.gamma.RI/ \*\*\*CD64\*\*\* transgenic model for in vivo analysis of ( \*\*\*bispecific\*\*\* ) antibody therapeutics.

AUTHOR: Heijnen I.A.F.M.; Van de Winkel J.G.J.

CORPORATE SOURCE: Department of Immunology, University Hospital Utrecht, Utrecht, Netherlands

SOURCE: Journal of Hematotherapy, (1995) 4/5 (351-356).  
ISSN: 1061-6128 CODEN: JOEMEL

COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 026 Immunology, Serology and Transplantation  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The human high-affinity IgG receptor, hFc.gamma.RI ( \*\*\*CD64\*\*\* ), is exclusively expressed on myeloid cells, where it serves an important role as a (cytotoxic) trigger molecule. To establish an in vivo model for analysis of the role of hFc.gamma.RI in immunity, we developed a novel transgenic mouse model. The human Fc.gamma.RIA gene, with endogenous regulatory sequences, was used to generate two lines of transgenic FVB/N mice. Immunohistochemical and flow cytometric studies showed that

hFc.gamma.RI expression was restricted to myeloid cells. Monocytes, macrophages, and polymorphonuclear neutrophils (PMN) expressed physiologic

hFc.gamma.RI levels, whereas lymphocytes and mast cells lacked expression.

Human Fc.gamma.RI expression was regulated in vivo by the cytokines IFN-.gamma. (exactly as in humans) and IL-10. The transgenic receptor proved functional and bound human \*\*\*tumor\*\*\* cells via anti-hFc.gamma.RI-based \*\*\*bispecific\*\*\* antibodies. hFc.gamma.RI could, furthermore, be efficiently targeted in vivo by \*\*\*CD64\*\*\* antibodies. These data demonstrate that the hFc.gamma.RI transgenic mouse model closely parallels the situation in humans. This mouse model seems useful for in vivo evaluation of the therapeutic potential of novel \*\*\*bispecific\*\*\* reagents in \*\*\*tumor\*\*\* and infection models.

L16 ANSWER 51 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95276531 EMBASE

DOCUMENT NUMBER: 1995276531

TITLE: [Oncogenes, growth factors and immunotherapy].  
ONKOGENE, WACHSTUMSFAKTOREN UND IMMUNTHERAPIE.

AUTHOR: Tesch H.

CORPORATE SOURCE: Klinik 1 fur Innere Medizin, Universitat Koln,  
Josef-Stelzmann-Strasse 9,D-50931 Koln, Germany

SOURCE: Onkologie, (1995) 18/SUPPL. 1 (4-10).

ISSN: 0378-584X CODEN: ONKOD2

COUNTRY: Germany

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 016 Cancer  
022 Human Genetics  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index

LANGUAGE: German

SUMMARY LANGUAGE: English; German

AB The development of malignant tumors occurs in several steps. Some of the events could be elucidated in the last years. Molecular analyses revealed genetic aberrations in the \*\*\*tumor\*\*\* cells. Genes that can transform

cells into \*\*\*tumor\*\*\* cells are called oncogenes. These genes are highly conserved during evolution and encode products that are essential for cell proliferation or differentiation. The genetic deregulation can lead to the altered production of cellular growth factors, signal transduction molecules or DNA binding transcription factors. The genetic alterations can be used today as molecular \*\*\*tumor\*\*\* -specific markers. Especially the polymerase chain reaction allows a very sensitive detection of residual \*\*\*tumor\*\*\* cells (1 in 1,000,000 cells). The identification, characterization and production of recombinant hematopoietic growth factors allowed new therapeutic strategies in the treatment of malignant tumors. These factors are used frequently after myelotoxic chemotherapy to reduce side effects. A variety of clinical studies demonstrated the efficacy of this treatment, which led to the reduction of infections; likewise, the use of antibiotics and the

duration

of hospitalization were diminished. In addition, the colony-stimulating factors allow a dose escalation of cytotoxic drugs and the recruitment of stem cells. Besides chemotherapy new immunotherapeutical strategies are currently analyzed with antibody conjugates or activation of T

lymphocytes

to achieve \*\*\*tumor\*\*\* -specific cell kill.

L16 ANSWER 52 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1993:656537 CAPLUS  
 DOCUMENT NUMBER: 119:256537  
 TITLE: Diagnostic and/or therapeutic immunoconjugates  
 targeted to neovascular endothelial cells  
 INVENTOR(S): Thorpe, Philip E.; Burrows, Francis J.  
 PATENT ASSIGNEE(S): University of Texas System, USA; Imperial Cancer  
 Research Technology  
 SOURCE: PCT Int. Appl., 171 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 9  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9317715	A1	19930916	WO 1993-US1956	19930305
W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9337378	A1	19931005	AU 1993-37378	19930305
EP 627940	A1	19941214	EP 1993-906289	19930305
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 6004554	A	19991221	US 1994-295868	19941202
PRIORITY APPLN. INFO.:			US 1992-846349	19920305
			WO 1993-US1956	19930305

AB An antibody or antibody fragment that recognizes a cell surface antigen  
 assocd. with endothelial vasculature of a vascularized \*\*\*tumor\*\*\*  
 mass is linked to a therapeutic or diagnostic agent for treatment or  
 diagnosis of vascularized tumors. The antibody may be linked to a  
 paramagnetic or radioactive ion, cytotoxic agent, cytokine, etc. Thus, a  
 neuroblastoma transfected with the mouse .gamma.-interferon gene was  
 grown  
 in mice with severe combined immunodeficiency. The .gamma.-interferon  
 secreted by the \*\*\*tumor\*\*\* induced expression of MHC class II  
 antigens on the \*\*\*tumor\*\*\* vascular endothelium. A rat IgG2b  
 monoclonal antibody which recognized MHC Ia antigens, conjugated to  
 deglycosylated ricin A chain, was used successfully for treatment of the  
 neuroblastoma.

L16 ANSWER 53 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 94011887 EMBASE  
 DOCUMENT NUMBER: 1994011887  
 TITLE: Targeting of T lymphocytes against EGF-receptor+  
 \*\*\*tumor\*\*\* cells by \*\*\*bispecific\*\*\* monoclonal  
 antibodies: Requirement of CD3 molecule cross-linking for  
 T-cell activation.  
 AUTHOR: Ferrini S.; Cambiaggi A.; Sforzini S.; Marciano S.;  
 Canevari S.; Mezzanzanica D.; Colnaghi M.I.; Grossi C.E.;  
 Moretta L.  
 CORPORATE SOURCE: Ist. Naz. per la Ricerca sul Cancro, V.le Benedetto XV  
 10,16132 Genoa, Italy  
 SOURCE: International Journal of Cancer, (1993) 55/6 (931-937).  
 ISSN: 0020-7136 CODEN: IJCNAW  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 016 Cancer

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Targeting of T lymphocytes against epidermal growth-factor receptor (EGF-R)+ \*\*\*tumor\*\*\* cells was achieved by constructing a hybrid hybridoma which secretes an anti-EGF-R/anti-CD3 \*\*\*bispecific\*\*\* monoclonal antibody (biMab) of hybrid isotype (IgG1/IgG(2a)).

## Purification

of biMab molecules from parental anti-EGF-R and anti-CD3 MAbs was performed by protein-A chromatography. The purified biMab was able to trigger the lysis of EGF-R+ \*\*\*tumor\*\*\* cell lines (A431, IGROV-I, MDA-468 and U-87) and of NIH-3T3 transfectants expressing human EGF-R by cytolytic T lymphocytes, but it was ineffective in the case of EGF-R-negative \*\*\*tumor\*\*\* targets. Mormal EGF-R+ cells (keratinocytes and endometrial cells) were also susceptible to biMab-targeted cytotoxicity. However, the amount of biMab required to induce half-maximal cytotoxicity of \*\*\*tumor\*\*\* cells over-expressing the EGF-R molecule (A431) was considerably lower than that required to induce lysis of EGF-R+ \*\*\*tumor\*\*\* or normal cells which express EGF-R at considerably lower density. The ability of such biMAbs to deliver activation signals to T cells was evaluated by Ca++ mobilization and lymphokine production experiments. The soluble anti-EGF-R/anti-CD3 biMab failed to induce intracellular Ca++ increases, which occurred only after cross-linking induced by an anti-mouse IgG antibody. Secretion of lymphokines (IFN- $\gamma$ , TNF- $\alpha$  and GM-CSF) was induced by contact of the biMab-coated effector cells with the relevant \*\*\*tumor\*\*\* target, whereas the soluble biMab was virtually ineffective. In addition, biMab-coated effector cells retained the ability to recognize and to lyse EGF-R+ \*\*\*tumor\*\*\* cells for a prolonged period of time. Our data indicate that activation of effector cells targeted by biMAbs can only occur at the \*\*\*tumor\*\*\* site, where cross-linking of surface CD3 molecules is induced by contact with the \*\*\*tumor\*\*\* cells.

L16 ANSWER 54 OF 64 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1993:456725 BIOSIS

DOCUMENT NUMBER: PREV199396101625

TITLE: T-cell retargeting using \*\*\*bispecific\*\*\* monoclonal antibodies in a rat colon carcinoma model: IV.  
\*\*\*Tumor\*\*\* neutralization in Winn type assays.

AUTHOR(S): Beun, Gideon D. M. (1); Van De Velde, Cornelis J. H.;  
Fleuren, Gert Jan; Eggermont, Alexander M. M.

CORPORATE SOURCE: (1) Dep. Hematol., Dr. Daniel den Hoed Cancer Cent.,  
Groene

SOURCE: Hilledijk 301, PO Box 5201, 3008 AE Rotterdam Netherlands  
Journal of Immunotherapy, (1993) Vol. 14, No. 1, pp. 11-15.

ISSN: 1053-8550.

DOCUMENT TYPE: Article

LANGUAGE: English

AB We investigated the ability of \*\*\*bispecific\*\*\* anti-T-cell receptor times antitumor antibodies, destined for the study of T-cell retargeting in a rat colon carcinoma model, to enhance \*\*\*tumor\*\*\* neutralization by polyclonally activated CD8+ T lymphocytes in hepatic subcapsular Winn type assays against syngeneic CC531 colon carcinoma cells. Attempts to improve on initially unsatisfactory results were guided by a 3-day in vitro cocultivation assay, demonstrating that recombinant IL-2 (rIL-2) at concentrations as low as 1 U/ml would promote \*\*\*tumor\*\*\* neutralization by retargeted effector cells. Accordingly, we found that a nontoxic regimen of rIL-2 administration, 200,000 U subcutaneously every



h for 3 days, strongly enhanced natural killer-like as well as retargeted anti- \*\*\*tumor\*\*\* activity in Winn assays and enabled retargeted effector cells to prevent \*\*\*tumor\*\*\* growth in the majority of animals. These results back up and direct future attempts to treat established \*\*\*tumor\*\*\* lesions.

L16 ANSWER (55) OF 64 CAPLUS COPYRIGHT 2000 ACS  
 ACCESSION NUMBER: 1992:406007 CAPLUS  
 DOCUMENT NUMBER: 117:6007  
 TITLE: Targeted immunostimulation with \*\*\*bispecific\*\*\* reagents  
 INVENTOR(S): Romet-Lemonne, Jean Loup; Fanger, Michael W.  
 PATENT ASSIGNEE(S): Medarex, Inc., USA  
 SOURCE: PCT Int. Appl., 21 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9205793	A1	19920416	WO 1991-US7283	19911004
W: AU, CA, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
CA 2093022	AA	19920406	CA 1991-2093022	19911004
AU 9188694	A1	19920428	AU 1991-88694	19911004
AU 667460	B2	19960328		
EP 553244	A1	19930804	EP 1991-919595	19911004
EP 553244	B1	19981230		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 06502410	T2	19940317	JP 1991-518279	19911004
AT 175118	E	19990115	AT 1991-919595	19911004
ES 2129029	T3	19990601	ES 1991-919595	19911004
PRIORITY APPLN. INFO.:			US 1990-593083	19901005
			WO 1991-US7283	19911004

AB Immune response against an antigen is stimulated by administering the antigen in conjunction with a binding agent (e.g. a heteroantibody) specific for an antigen-presenting cell, e.g. a \*\*\*macrophage\*\*\*.

The binding agent specifically binds a receptor of the antigen-presenting cell, such as an Fc receptor, without being blocked by the endogenous ligand for the receptor. A \*\*\*bispecific\*\*\* heteroantibody was prepd. from a monoclonal antibody against human erythrocytes (mono-D, a human anti-RhD antibody) and anti-Fc.gamma.RI antibody 32 (Fc.gamma.RI is the high affinity Fc receptor). The heteroantibody was incubated with erythrocytes, and the heteroantibody-coated erythrocytes were then incubated with adherent monocytes (macrophages). The heteroantibody triggered internalization of the antigen by the macrophages. Enhanced tetanus toxoid presentation by directing tetanus toxoid to human Fc.gamma.R is also described.

L16 ANSWER 56 OF 64 MEDLINE  
 ACCESSION NUMBER: 93090873 MEDLINE  
 DOCUMENT NUMBER: 93090873  
 TITLE: Biology and therapy with biologic agents in gynecologic \*\*\*cancer\*\*\*.  
 AUTHOR: Wiener J R; Berchuck A; Bast R C Jr

CORPORATE SOURCE: Department of Obstetrics and Gynecology, Duke University  
Medical Center, Durham, NC 27710..  
SOURCE: CURRENT OPINION IN ONCOLOGY, (1992 Oct) 4 (5) 946-54.  
Ref:

52

Journal code: A1V. ISSN: 1040-8746.

PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199303

AB Growth of epithelial ovarian \*\*\*cancer\*\*\* is influenced by several factors including transforming growth factor-alpha and transforming growth factor-beta, \*\*\*macrophage\*\*\* colony stimulating factor, \*\*\*tumor\*\*\* necrosis factor-alpha, interleukin-1 and interleukin-6, c-erb B-2 (HER-2/neu), and mutant p53. Continued expression of the epidermal growth factor receptor, new expression of c-fms, and overexpression of HER-2/neu are associated with a poor prognosis. A number of cytokines have been used to treat patients with ovarian \*\*\*cancer\*\*\*, including interferon-alpha, interferon-gamma, \*\*\*tumor\*\*\* necrosis factor-alpha, and interleukin-2. Judging from preclinical models, interferon-gamma may be more active than interferon-alpha against human ovarian \*\*\*cancer\*\*\*. Although \*\*\*tumor\*\*\* necrosis factor-alpha can stimulate proliferation of some ovarian cancers, the cytotoxic activity of \*\*\*tumor\*\*\* necrosis factor-alpha has been amplified ex vivo by inhibitors of protein synthesis. Similar heterogeneity exists with regard to interleukin-1 where stimulation or inhibition of cell proliferation has been observed. \*\*\*Tumor\*\*\* -infiltrating lymphocytes from ascites fluid contain cells capable of major histocompatibility complex-restricted and major histocompatibility complex-nonrestricted cytotoxicity. \*\*\*Tumor\*\*\* -infiltrating lymphocytes and interleukin-2 have been combined with cytotoxic chemotherapy to treat advanced or recurrent disease. \*\*\*Bispecific\*\*\* monoclonal antibodies that react both with T cells and ovarian \*\*\*tumor\*\*\* cells have produced \*\*\*tumor\*\*\* inhibition in human \*\*\*tumor\*\*\* xenografts. Immunotoxins that contain OVB3 and pseudomonas exotoxin have been evaluated in a phase I clinical trial. Dose-limiting central neurotoxicity has been observed without \*\*\*tumor\*\*\* regression. A monoclonal antibody designated OVX1 has been developed against a high-molecular-weight mucinlike molecule associated with ovarian cancers. (ABSTRACT TRUNCATED AT 250 WORDS)

L16 ANSWER 57 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 92070545 EMBASE

DOCUMENT NUMBER: 1992070545

TITLE: Adoptive immunotherapy with \*\*\*bispecific\*\*\* antibodies: Targeting through macrophages.

AUTHOR: Chokri M.; Girard A.; Borrelly M.C.; Oleron C.; Romet-Lemonne J.L.; Bartholeyns J.

CORPORATE SOURCE: Centre National de Transfusion Sanguine, 3 Avenue des

SOURCE: Tropiques, 91943 Les Ulis Cedex, France  
Research in Immunology, (1992) 143/1 (95-99).  
ISSN: 0923-2494 CODEN: RIMME5

COUNTRY: France

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We report on two applications of \*\*\*bispecific\*\*\* antibodies to enhance the antitumoral function of human macrophages: (1) use of rhuIFN.gamma. (recombinant human IFN.gamma.) encapsulated in human red blood cells coated with anti-Fc.gamma.RI/anti-RhD+ \*\*\*bispecific\*\*\* antibodies to target and to activate human macrophages; encapsulated rhuIFN.gamma. was more potent than free IFN.gamma. in activating mature macrophages in vitro, demonstrating the efficacy of this delivery system to initiate in situ activation of macrophages and also to maintain a high antitumoral efficacy of macrophages with less side effects than after systemic injection of IFN.gamma.; (2) targeting of activated macrophages to tumours by \*\*\*bispecific\*\*\* antibodies directed against \*\*\*macrophage\*\*\* Fc.gamma.RI and against human adenocarcinoma

antigen;

differentiated human macrophages became cytotoxic for human adenocarcinoma

in vitro and in vivo (tumours implanted in nude mice) when activated by rhuIFN.gamma. this effect was increased in the presence of

\*\*\*bispecific\*\*\* antibodies. These two approaches were aimed at increasing the efficacy of cellular immunotherapies using activated macrophages as effector cells ( \*\*\*macrophage\*\*\* -activated killer, or MAK), an adoptive therapy which we have developed. \*\*\*Bispecific\*\*\* antibodies could increase specific homing and activation of cytotoxic MAK effectors at tumour sites.

L16 ANSWER 58 OF 64 MEDLINE

ACCESSION NUMBER: 92229078 MEDLINE

DOCUMENT NUMBER: 92229078

TITLE: Functional consequences of monocyte/ \*\*\*macrophage\*\*\* infection by HIV1.

AUTHOR: Le Naour R; Raoul H; Mabondzo A; Ripoll L; Bartholeyns J; Romet-Lemonne J L; Dormont D

CORPORATE SOURCE: Laboratoire de Neuropathologie experimentale et Neurovirologie, Commissariat `a l'Energie Atomique, CRSSA/DSV/DPTE, Fontenay-aux-Roses, France.

SOURCE: RESEARCH IN IMMUNOLOGY, (1992 Jan) 143 (1) 49-56.  
Journal code: R6E. ISSN: 0923-2494.

PUB. COUNTRY: France

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199207

AB Monocyte/ \*\*\*macrophage\*\*\* infection by human immunodeficiency virus type 1 (HIV1) was studied for its effects on the production of tumour necrosis factor alpha (TNF alpha) and the expression of the manganese superoxide dismutase (MnSOD) gene. For this purpose, human peripheral blood monocytes were obtained from healthy HIV1-seronegative donors by centrifugal elutriation and infected with either the HIV1/LAV1 strain or with the primary HIV1/DAS isolate. The results showed that (1) HIV1/LAV1-infected macrophages did not produce any biologically detectable

TNF alpha during the few hours following lentiviral infection, despite rises in the TNF alpha mRNA level; (2) MnSOD gene transcription in the macrophages increased, as measured 2 and 4 h after infection; (3) the level of the MnSOD gene expression declined during the late phases of lentiviral infection, but TNF alpha synthesis and gene expression rose; and (4) \*\*\*bispecific\*\*\* antibody comprised of anti-Fc gamma RI (anti-\*\*\*CD64\*\*\* ) and anti-gp41 monoclonal antibodies inhibited the in vitro infection of monocyte-derived macrophages by HIV1/DAS.

L16 ANSWER (59) OF 64 CAPLUS COPYRIGHT 2000 ACS  
 ACCESSION NUMBER: 1991:490564 CAPLUS  
 DOCUMENT NUMBER: 115:90564  
 TITLE: \*\*\*Bispecific\*\*\* heteroantibodies with dual effector functions  
 INVENTOR(S): Fanger, Michael W.; Guyre, Paul M.; Ball, Edward D.  
 PATENT ASSIGNEE(S): Medarex, Inc., USA  
 SOURCE: PCT Int. Appl., 26 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9105871	A1	19910502	WO 1990-US5981	19901018
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
CA 2069960	AA	19910421	CA 1990-2069960	19901018
JP 05505595	T2	19930819	JP 1991-500408	19901018
EP 595798	A1	19940511	EP 1990-917241	19901018
EP 595798	B1	19990303		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 177152	E	19990315	AT 1990-917241	19901018
ES 2133139	T3	19990901	ES 1990-917241	19901018
US 6071517	A	20000606	US 1994-359931	19941220
PRIORITY APPLN. INFO.:			US 1989-424540	19891020
			US 1986-882181	19860707
			US 1987-69412	19870701
			US 1988-151450	19880202
			WO 1990-US5981	19901018
			US 1992-972871	19921104
			US 1994-226388	19940412

AB \*\*\*Bispecific\*\*\* antibodies which react both with the high-affinity Fc.gamma. receptor ( \*\*\*CD64\*\*\* antigen) of human effector cells and with a target cell surface antigen are disclosed. Binding of the mols. to the Fc receptors found on effector cells is not blocked by human IgG. The mols. are useful for targeting human effector cells (e.g. macrophages) against cells bearing this target antigen. For this purpose, \*\*\*bispecific\*\*\* mols. can be constructed contg. the binding region derived from an anti-Fc.gamma. receptor antibody and the binding region derived from an antibody specific for the target antigen. Targeted effector cells can be used to destroy cells bearing the target cell surface antigen by cell-mediated antibody-dependent cytotoxicity and by complement-fixation. Thus, Fab from a monoclonal antibody to the human monocyte high-affinity receptor was conjugated to monoclonal IgM to the

CD15 cell-surface antigen. Monocytes, HL-60 leukemia cells, and the heteroantibody were incubated together for 18 h at 37.degree.. Monocytes alone caused 5-20% killing, monocytes plus heteroantibody caused 20-50% killing, and monocytes plus heteroantibody plus human serum caused 50-80% killing.

L16 ANSWER 60 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1991:464752 CAPLUS

DOCUMENT NUMBER: 115:64752

TITLE: Anti-Rh(D) heteroantibodies and pharmaceutical composition containing same for drug targeting and therapy using macrophages

INVENTOR(S): Fanger, Michael; Lazard, Florence; Romet-Lemonne, Jean

PATENT ASSIGNEE(S): Loup  
Fondation Nationale de Transfusion Sanguine, Fr.  
SOURCE: PCT Int. Appl., 22 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9105800	A1	19910502	WO 1990-FR757	19901019
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
FR 2653561	A1	19910426	FR 1989-13678	19891019
PRIORITY APPLN. INFO.:			FR 1989-13678	19891019
AB Chimeric antibodies comprise all or part of anti-Rh(D) blood-group substance antibody linked with all or part of an antibody to a receptor for Fc fragment of Igs that is not blocked by IgG. These chimeric antibodies are bound to erythrocytes encapsulating, e.g. ***macrophage*** activators, antiinfective agents, and anticancer agents, via the Rh(D) surface antigen on the erythrocytes, and the complexes target macrophages and are thus useful in therapies involving macrophages. The F(ab') <sub>2</sub> fragment of monoclonal antibody H2D5D2 (anti D) was coupled to the FAb' fragment of monoclonal antibody 32.2 (anti Fc.gamma.RI). This chimeric antibody was reacted with Rh-pos. erythrocytes loaded with .gamma. interferon. U937 ***tumor*** cells were inhibited using human macrophages and the complex.				

L16 ANSWER (61) OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1991:677836 CAPLUS

DOCUMENT NUMBER: 115:277836

TITLE: Fc receptors for IgG (Fc.gamma.Rs) on human monocytes and macrophages are not infectivity receptors for human immunodeficiency virus type 1 (HIV-1): studies using \*\*\*bispecific\*\*\* antibodies to target HIV-1 to various myeloid cell surface molecules, including the Fc.gamma.R

AUTHOR(S): Connor, R. I.; Dinces, N. B.; Howell, A. L.;  
Romet-Lemonne, J. L.; Pasquali, J. L.; Fanger, M. W.  
CORPORATE SOURCE: Dep. Microbiol., Dartmouth Med. Sch., Hanover, NH,  
03756, USA

SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1991), 88(21), 9593-7

CODEN: PNASA6; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Fc.gamma.Rs (Fc.gamma.RI, Fc.gamma.RII, and Fc.gamma.RIII) are highly expressed on human mononuclear phagocytes and function in the clearance of

immune complexes and opsonized pathogens. The authors examd. the role of Fc.gamma.R in mediating antibody-dependent clearance of HIV-1 by human monocytes and monocyte-derived macrophages by using \*\*\*bispecific\*\*\* antibodies (BsAbs) to independently target the virus to Fc.gamma.RI, Fc.gamma.RII, or Fc.gamma.RIII. Virus prodn. was markedly reduced in monocytes cultured with strain HIV-1IIIB opsonized with BsAbs that target the virus to either Fc.gamma.RI or Fc.gamma.RII compared to monocytes cultured with virus in the absence of BsAbs or in the presence of BsAbs that target the virus to non-Fc.gamma.R surface antigens (CD33 and HLA-A,B,C). These results were confirmed using the monotropic isolate HIV-1JRFL. Interaction of HIV-1JRFL with Fc.gamma.RII on human monocytes and Fc.gamma.RI, Fc.gamma.RII, or Fc.gamma.RIII on monocyte-derived macrophages resulted in markedly reduced levels of virus prodn. in these cultures. Moreover, HIV-1 infection of monocytes and monocyte-derived macrophages was completely blocked by anti-CD4 monoclonal antibodies, indicating that interaction with CD4 is required for infectivity even under conditions of antibody-mediated binding of HIV-1 to Fc.gamma.R. Thus, it is proposed that highly opsonized HIV-1 initiates high-affinity multivalent interactions with Fc.gamma.R that trigger endocytosis and intracellular degrdn. of the antibody-virus complex. At lower levels of antibody opsonization, there are too few interactions with Fc.gamma.R to initiate endocytosis and intracellular degrdn. of the antibody-virus complex, but there are enough interactions to stabilize the virus at the cell surface, allowing antibody-dependent enhancement of HIV-1 infection through high-affinity CD4 interactions. However, interaction of highly opsonized HIV-1 with Fc.gamma.Rs through BsAbs may reduce viral infectivity through Fc.gamma.R-mediated cytotoxic mechanisms and, therefore, BsAbs offer promise as therapeutic reagents in HIV-1 infections.

L16 ANSWER 62 OF 64 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 91305895 EMBASE

DOCUMENT NUMBER: 1991305895

TITLE: \*\*\*Bispecific\*\*\* antibodies and targeted cellular cytotoxicity: Therapeutic hopes confirmed.

AUTHOR: Bauer T.; Drakeman D.L.

CORPORATE SOURCE: Ctre Nat de Transfus Sanguine, F-7500 Paris, France

SOURCE: Vox Sanguinis, (1991) 61/2 (156-157).

ISSN: 0042-9007 CODEN: VOSAAD

COUNTRY: Switzerland

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 016 Cancer

025 Hematology

026 Immunology, Serology and Transplantation

037 Drug Literature Index

LANGUAGE: English

L16 ANSWER 63 OF 64 MEDLINE

DUPLICATE 2

ACCESSION NUMBER: 90347203 MEDLINE

DOCUMENT NUMBER: 90347203

TITLE: Evaluation of the antibody-dependent cytotoxic capabilities

of individual human monocytes. Role of Fc gamma RI and Fc gamma RII and the effects of cytokines at the single cell level.

AUTHOR: Connor R I; Shen L; Fanger M W

CORPORATE SOURCE: Department of Microbiology, Dartmouth Medical School,  
Hanover, NH 03756..  
CONTRACT NUMBER: AI 19058 (NIAID)  
CA 44794 (NCI)  
AI 22816 (NIAID)  
+  
SOURCE: JOURNAL OF IMMUNOLOGY, (1990 Sep 1) 145 (5) 1483-9.  
Journal code: IFB. ISSN: 0022-1767.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer  
Journals  
ENTRY MONTH: 199011

AB In this report we present evidence that not all human peripheral blood monocytes mediate antibody-dependent cellular cytotoxicity (ADCC), and that this function may be determined on an individual cell by both the type and level of expression of FcR, and by the state of cellular activation and/or differentiation. Although the diverse range of effector and regulatory functions performed by human monocytes suggests the possibility of distinct subsets, it is not clear whether observed functional heterogeneity reflects the presence of true monocyte subpopulations, or whether this diversity represents a continuum of maturational states present in the peripheral circulation. In an attempt to address this question, we investigated the ability of human monocytes to carry out ADCC at the single cell level, with emphasis on the role of the three FcR for IgG (Fc gamma RI, Fc gamma RII, and Fc gamma RIII) in mediating cytotoxicity. Using a modified plaque assay, 58.3% +/- 4.9 of freshly isolated monocytes mediated ADCC, as evidenced by the formation

of lytic plaques in monolayers of ox erythrocyte (oxE) target cells. Significant increases in the number of plaque-forming cells were observed after positive selection by flow microfluorimetry for those monocytes expressing high levels of Fc gamma RI and Fc gamma RII, but not Fc gamma RIII. \*\*\*Bispecific\*\*\* antibodies composed of Fab fragments of anti-oxE antibody covalently coupled to Fab fragments of anti-Fc gamma R antibodies were used to independently evaluate the ability of Fc gamma

RI, Fc gamma RII, and Fc gamma RIII to mediate single cell cytotoxicity. Significant increases in the number of plaque-forming cells were observed in the presence of anti-Fc gamma RI x anti-oxE and anti-Fc gamma RII x anti-oxE \*\*\*bispecific\*\*\* antibodies, confirming the efficiency of Fc gamma RI and Fc gamma RII as cytotoxic trigger molecules on human monocytes. Incubation of monocytes with purified rIFN-gamma and granulocyte \*\*\*macrophage\*\*\* -CSF, but not IL-2, IL-3, IL-4, IL-6, or TNF-alpha, also resulted in significant increases in the number of monocytes mediating cytotoxicity, suggesting that cytotoxic ability at

the single cell level may be influenced by factors which effect monocyte activation and differentiation, respectively. Overall, these studies demonstrate that freshly isolated human monocytes are heterogeneous in their ability to mediate ADCC, and suggest that this functional diversity arises not from discrete subpopulations of cells, but from a continuum of maturational/activational states present within the peripheral circulation.

L16 ANSWER 64 OF 64 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1991:533439 CAPLUS

DOCUMENT NUMBER: 115:133439

TITLE: Targeting of cytotoxic cells against tumors with

heterocrosslinked, \*\*\*bispecific\*\*\* antibodies  
AUTHOR(S): Segal, David M.; Qian, Jia Hua; Garrido, Maria A.;  
Perez, Pilar; Winkler, David F.; Wunderlich, John R.;  
Snider, Denis P.; Valdayo, Maria J.; Titus, Julie A.  
CORPORATE SOURCE: Exp. Immunol. Branch, Natl. Cancer Inst., Bethesda,  
MD, 20892, USA  
SOURCE: Proc. Int. Symp. Princess Takamatsu Cancer Res. Fund  
(1989), Volume Date 1988, 19th(Immune Syst. Cancer),  
323-31  
CODEN: PPTCBY  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
AB A review with 21 refs. on the use of crosslinked antibodies, with  
specificity for both \*\*\*tumor\*\*\* antigens and cytotoxic cell  
receptor,  
in the targetting of cellular cytotoxicity.